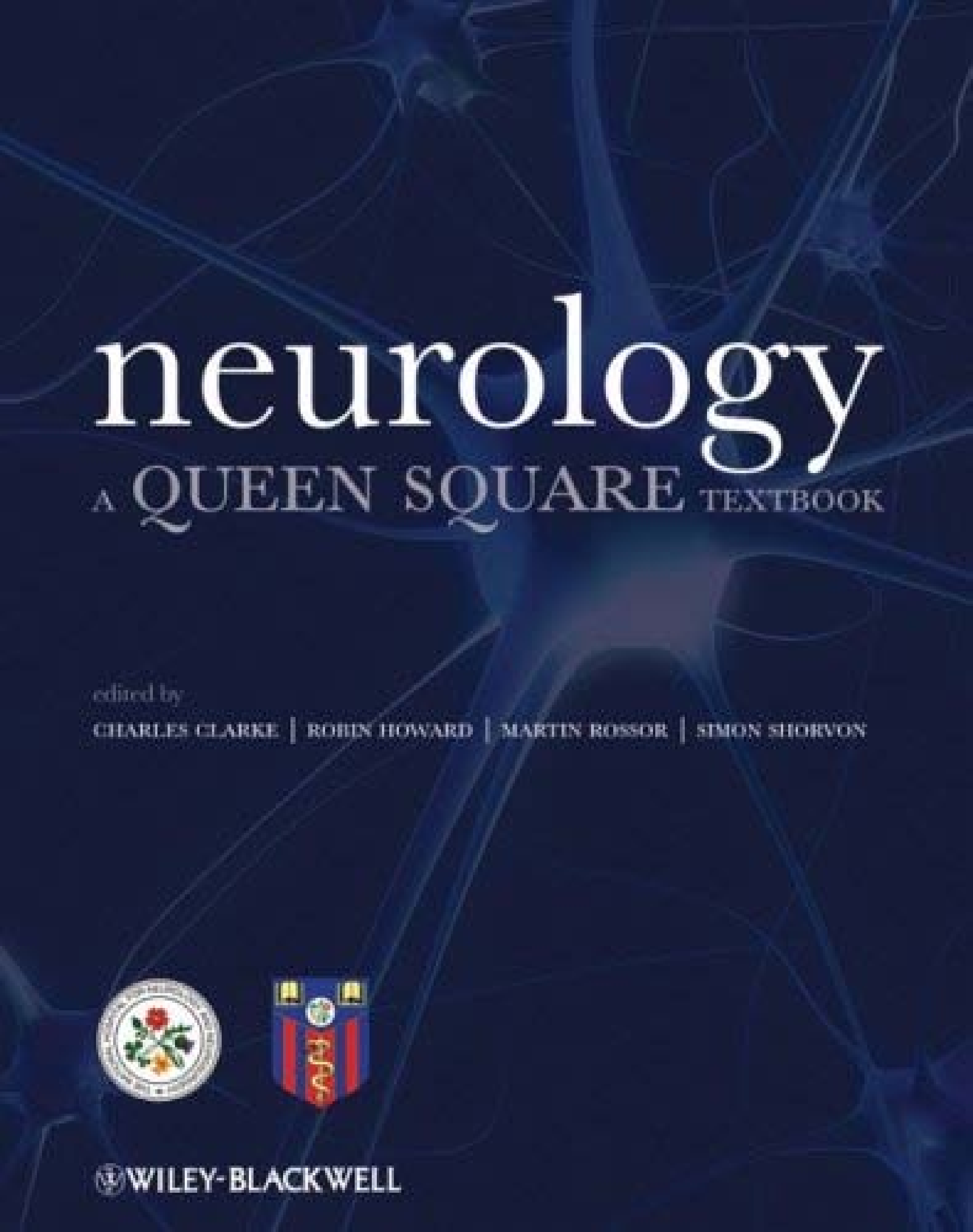

neurology

A QUEEN SQUARE TEXTBOOK

edited by

CHARLES CLARKE | ROBIN HOWARD | MARTIN ROSSOR | SIMON SHORVON

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Neurology

A Queen Square Textbook

Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard,
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ISBN: 978-1-405-13443-9

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Neurology

A Queen Square Textbook

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WILEY-BLACKWELL
A John Wiley & Sons, Ltd., Publication

This edition first published 2009, © 2009 by Blackwell Publishing Ltd

Blackwell Publishing was acquired by John Wiley & Sons in February 2007. Blackwell's publishing program has been merged with Wiley's global Scientific, Technical and Medical business to form Wiley-Blackwell.

Registered office: John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial offices: 9600 Garsington Road, Oxford, OX4 2DQ, UK
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
111 River Street, Hoboken, NJ 07030-5774, USA

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Library of Congress Cataloging-in-Publication Data

Neurology : a Queen Square textbook / edited by Charles Clarke . . . [et al.]. – 1st ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-4051-3443-9 (alk. paper)
1. Nervous system–Diseases–Textbooks. 2. Neurology–Textbooks. I. Clarke, Charles (Charles R. A.) II. National Hospital for Neurology and Neurosurgery (London, England) III. Institute of Neurology, Queen Square.
[DNLM: 1. Nervous System Diseases. 2. Neurology. WL 140 N492687 2009]
RC346.N44 2009
616.8–dc22
2008015538

ISBN: 978-1-4051-3443-9

A catalogue record for this book is available from the British Library.

Set in 9.25/12pt Minion by SNP Best-set Typesetter Ltd., Hong Kong
Printed and bound in Singapore by COS Printers Pte Ltd
First published 2009
1 2009

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Beginnings

A conversation with Professor Ian McDonald

Ian McDonald[1] kindly agreed to write the foreword for this book. Sadly, he died shortly before it was completed. We had met in Queen Square in 2004 to discuss what I had in mind, an integrated, practical textbook from the National Hospital and the Institute of Neurology.

'That is quite splendid', Ian had replied when I explained the nature of our project. 'Of course', he continued: 'a book like this has never been produced previously, and I think no one has been able to draw together the different personalities here – and that will not be at all easy . . .'.

Ian went on: 'Charlie Symonds[2] once told me that he had suggested a similar project to the National Hospital Medical Committee in the late 1930s'. Dr Charles Symonds' proposal had received an immediate veto from his senior colleague Dr Samuel Kinnier Wilson[3]: 'Dr Symonds there is no place for *that*. I have already written the definitive book, there is no need for another', Kinnier Wilson is said to have responded, acidly.

True, this present book came to fruition slowly. The authors are busy people, distinguished in specialist fields, but they have come together to produce this volume. The editors are most grateful to them all.

During the last five decades, neurology has progressed immeasurably and Queen Square has become a truly international centre. The editors have tried to integrate this international dimension, drawing on clinical experience and perspectives from Australia, Canada, China, Europe, India and USA. We thank our international editors for their comments and guidance.

We hope *Neurology: A Queen Square Textbook* achieves its object – to reflect the clinical practice of neurology as we know it and to illustrate the approach we teach and follow at the National Hospital for Neurology & Neurosurgery and the Institute of Neurology, Queen Square.

We all have valued Ian McDonald's encouragement and hope that if he were still with us, he would feel the finished product was worthy of the institutions and teachers that have guided our thoughts and practice over the years.

Charles Clarke
Queen Square
London WC1

---

[1] Professor Ian McDonald (1933–2006) was Professor of Neurology from 1978 to 1998. One of his great legacies remains his research into multiple sclerosis; his humanity, warmth and civility provide enduring memories for his students, colleagues and friends throughout the world.

[2] Sir Charles Symonds, KBE, CB (1890–1978) was appointed physician to *The National* in 1926. A selection of his many papers entitled *Studies in Neurology* was published in 1970.

[3] Dr Samuel Kinnier Wilson (1878–1937) was appointed physician to *The National* in 1912. He had written the seminal paper on Progressive Hepato-Lenticular Degeneration shortly before this. *Neurology*, his famous textbook, was published posthumously in 1940.

Foreword

Queen Square in Bloomsbury, London, is known the world over as a centre for neurology and clinical neuroscience. Like many institutions, *The National*, initially The National Hospital for the Relief and Cure of the Paralysed and Epileptic, was founded through the hard work and generosity of people with a broad sense of charitable intent, especially the Chandler family – Johanna Chandler, her sister Louisa and their brother Edward. The doors of the original building opened in Queen Square in 1860. Dr Jabez Spence Ramskill was the first physician appointed, followed shortly by Dr Charles Brown-Séquard. Since 1860 there has been an unbroken record of progress across the clinical neurosciences. The names of all those who contributed in those early years are too numerous to mention, but amongst those who stand out today in an historical perspective are Dr Charles Brown-Séquard, Dr John Hughlings Jackson, Sir William Gowers, Sir David Ferrier, Sir Victor Horsley, Sir Gordon Holmes, Dr Samuel Kinnier Wilson, Sir Francis Walshe, Sir Charles Symonds and Dr Macdonald Critchley.

The National Hospital has undergone many changes and revolutionised its approach, for example towards neurological rehabilitation and brain injury, and has developed close and inseparable links with the Institute of Neurology, which has helped to promote research at Queen Square in both basic and clinical sciences. Both Hospital and Institute are now involved in advancing an extensive range of developments in translational medicine that are transforming the treatment of neurological diseases. These developments are reflected in this book.

The Institute of Neurology

The Institute of Neurology was established in 1950 and has been part of University College London since 1997. The Institute provides research and teaching of the highest quality in neurosciences, and professional training for clinical careers in neurology, neurosurgery, neuropsychiatry, neuroradiology, neuropathology and clinical neurophysiology. With its concentration of clinical and applied scientific activity, the Institute provides a unique national resource for both postgraduate training and research in the basic neurosciences and its associated clinical disciplines. The Institute currently holds active grants for research into the causes and treatment of a wide range of neurological diseases, including movement disorders, multiple sclerosis, epilepsy, brain cancer, stroke and brain injury, muscle and nerve disorders, cognitive dysfunction and dementia; the work of the Institute's clinical academic staff remains closely integrated with the Hospital.

The National Hospital for Neurology & Neurosurgery today

The National, now part of University College London Hospitals NHS Foundation Trust, is a thriving hospital, largely refurbished behind the 1890 façade. The hospital receives over 1000 new outpatient referrals each month and has over 200 beds, a dedicated ITU, extensive rehabilitation services and all ancillary departments in the most substantial specialist neurological hospital within the UK. The hospital provides the surrounding district general hospitals with specialist services. Many of the consultant staff continue to hold appointments that are linked to both general hospitals, the Institute of Neurology and *The National* itself. This maintains unique contact between the disciplines of research and clinical practice.

Neurology: A Queen Square Textbook

This book, the first of its kind to come from these two institutions, has a distinctly clinical flavour. It has been written very largely by clinicians, each in the forefront of their field, and focuses on the practical aspects of diagnosis, treatment and patient care. The book also provides an introduction to the basic sciences of neurology, of increasing importance in medical practice. It has been a pleasure to be one of the contributing authors.

Professor Roger Lemon PhD FMedSci
Sobell Chair of Neurophysiology & Director, Institute of Neurology
(2002–2008)

Preface

All Editors, Authors and Specialist Advisory Editors of *Neurology: A Queen Square Textbook* hold or recently held consultant or equivalent posts at the National Hospital for Neurology & Neurosurgery and/or the Institute of Neurology, Queen Square.

The National Hospital is part of University College London Hospitals NHS Foundation Trust, and the Institute of Neurology part of University College London.

The twenty Co-ordinating Authors organised individual chapters, encouraged and liaised with over 70 contributors and with them wrote this book.

The Specialist Advisory Editors gave invaluable advice and guidance in their respective fields. To ensure a worldwide perspective, the six International Regional Editors, all of whom have had close connections with Queen Square, provided advice and comment.

This book is an attempt to provide a fresh and up-to-date approach to the fascinating subject of neurology. We encouraged each author to relate their own clinical experience but, in order to achieve a degree of consistency, we took a robust overview of the important specialities within neurology and their relevance. Each chapter has been coordinated by an expert in the field, to give the reader an overall grasp of each major subject, indicating where developments within neurosciences fit into a broader picture.

The limited size of this book means that it has not been possible to provide references for all material. With the growth of information technology, a wealth of detailed sources are readily available.

We are most grateful to all those who have helped in this joint venture.

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Robin Howard
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Acknowledgements

We know that the skills of clinical practice are handed down, both by teachers and role models. The editors wish to thank all those who have taught, advised and inspired them – in many aspects of neurology and its related disciplines, in neuroscience and in research. When we came to list these many individuals, we soon realised we would be unable to mention each by name. Instead, we trust that those who read this book will understand how much the editors and authors owe to others. We hope we can pass on some of that knowledge and experience.

We thank our publishers, Wiley-Blackwell, and especially Helen Harvey (Project Manager), Rob Blundell (Development Editor), Martin Sugden (Publisher), who, having accepted that the project was viable, have waited for and worked on the draft manuscripts with unstinting patience. David Gardner, in Cyprus and Best-set, Hong Kong have transformed the draft illustrations into a coherent sequence, to make the finished product one that has truly crossed national boundaries. The authors have worked hard, for no personal reward and, despite numerous requests for text, diagrams and amendments, have remained firmly behind this project.

Secretarial help has also been invaluable, and amongst those who have contributed over and above their normal duties, we thank especially Claire Bloomfield, Wyn Jagger and Mary Wright.

The Rockefeller Library has provided its valuable resources, both historical and current. The Audio Visual Services Unit has been most helpful with the sourcing of some of the figures and photographs.

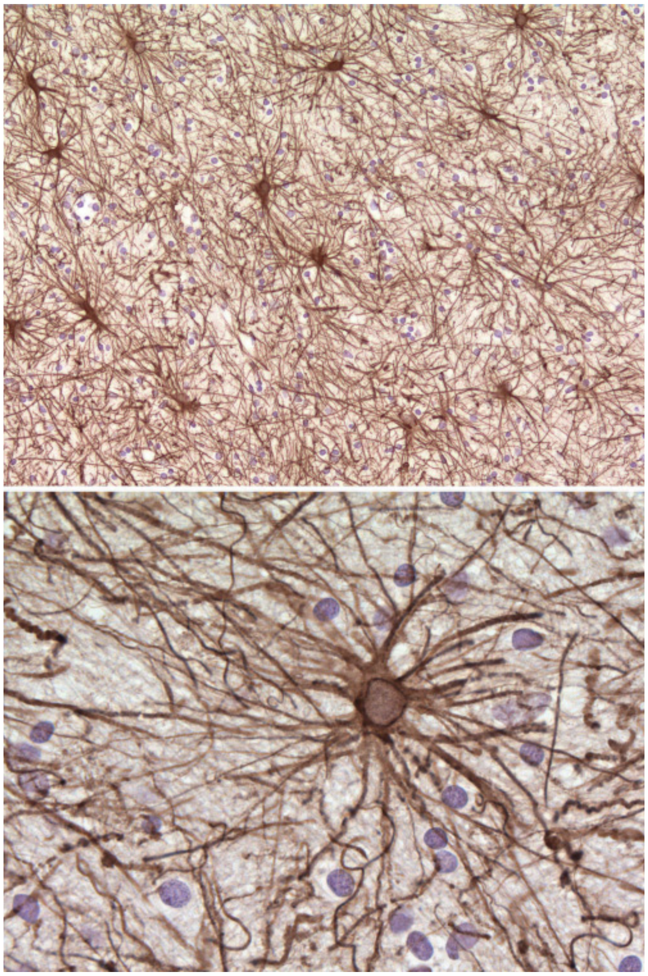

Plate 2.1 Astrocytes.

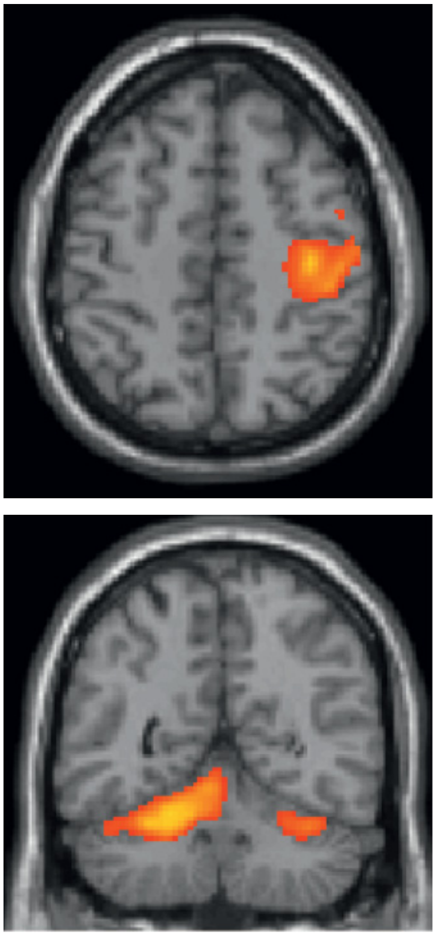

Plate 2.2 Cortical and cerebellar fMRI with voluntary activity of left hand (button press). Task-related activation can be seen in the contralateral hand region of primary sensorimotor cortex on the axial image and in the ipsilateral contralateral lobule VI of the cerebellum on the coronal image (Courtesy Dr Alex Leff, Wellcome Trust Centre for Neuroimaging, Institute of Neurology).

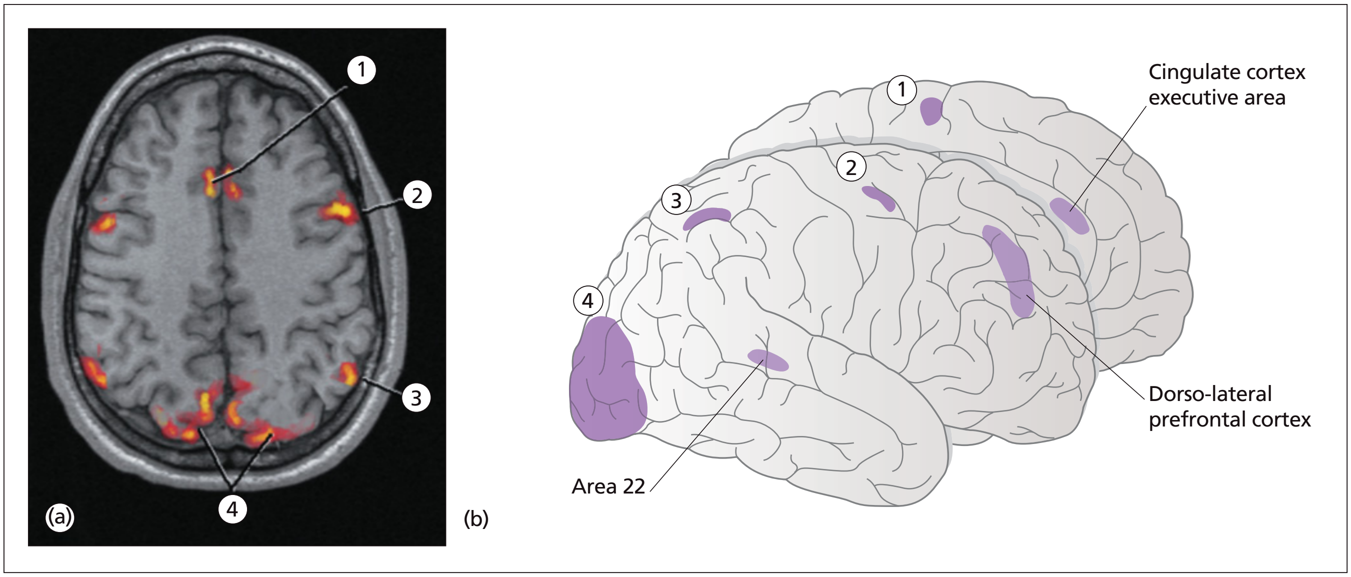
1
2
3
4
(a)
(b)
Cingulate cortex executive area
Dorso-lateral prefrontal cortex
Area 22

Plate 2.3 Functional MRI (a) and diagram (b) indicating cortical eye fields. 1. Supplementary eye field. 2. Frontal eye field. 3. Parietal eye field. 4. Occipital cortex.

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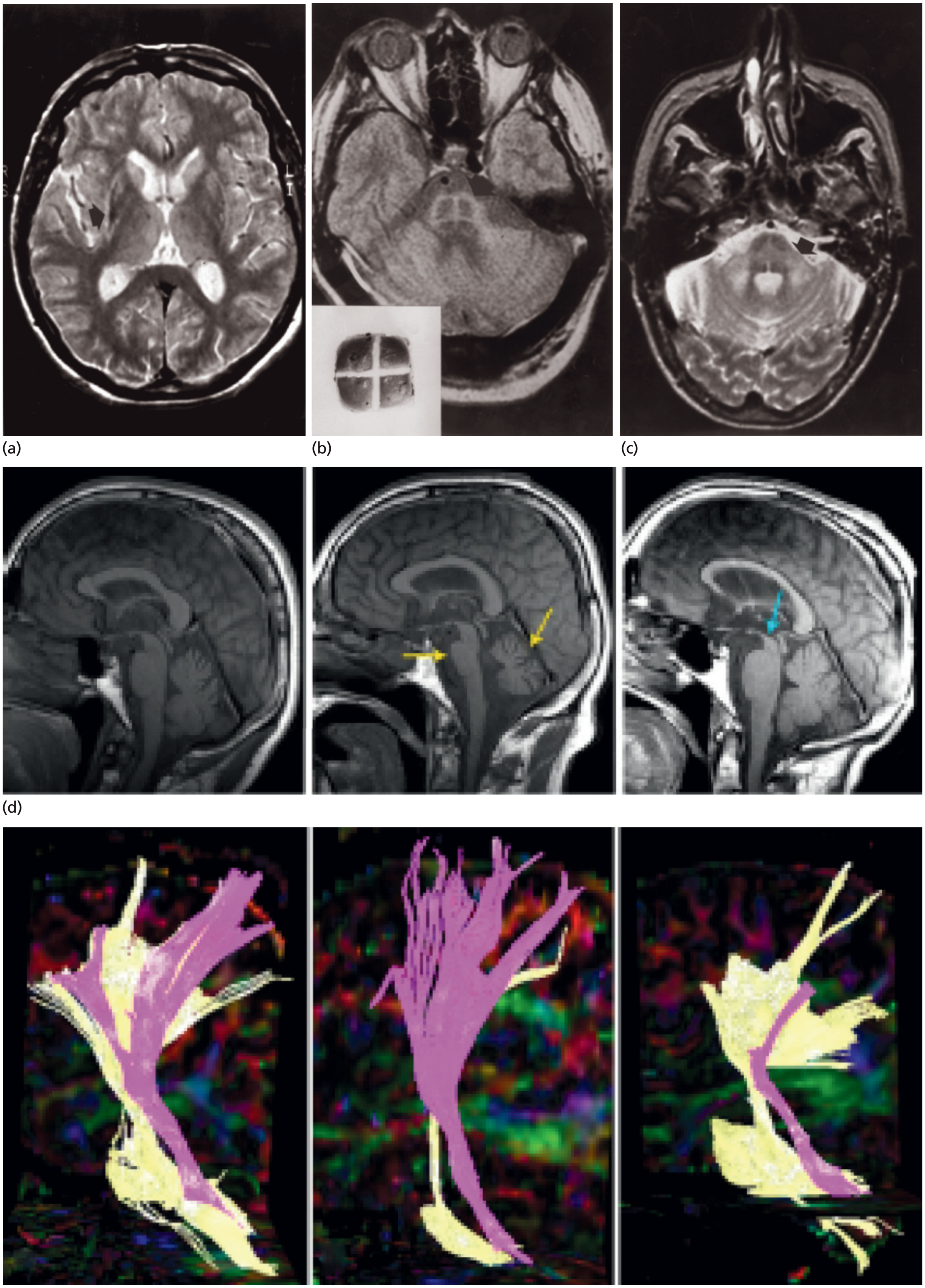
ISBN: 978-1-405-13443-9



(a) (b) (c)

(d)

(e)

Plate 5.1 MRI findings in Parkinson's disease (PD), multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). (a) Putaminal atrophy, hyperintense rim (arrow) and putaminal hypointensity (relative to globus pallidus) on T2-weighted images (1.5 T) in a patient with MSA. (b) T2-weighted images (0.5 T) showing 'hot cross bun' sign (inset shows a real hot cross bun) in a patient with MSA. (c) Infratentorial atrophy and signal change in pons, middle cerebellar peduncles (arrow) and cerebellum on T2-weighted images (0.5 T) in a patient with MSA. (d) Sagittal images in patients with (left to right) PD, MSA and PSP, showing atrophy of pons and cerebellum (arrows) in MSA and atrophy of midbrain (arrow – the 'hummingbird sign'). (e) Tractography (3 T) of the middle cerebellar peduncle (MCP, yellow) and superior cerebellar peduncle (SCP, purple) in patients with (left to right) PD, MSA and PSP, showing selective atrophy of MCP in MSA and of SCP in PSP. (Figure 5.1(a–c) from Schrag *et al.* 1998 and (d,e) from Nilsson *et al.* 2007 with permission.)

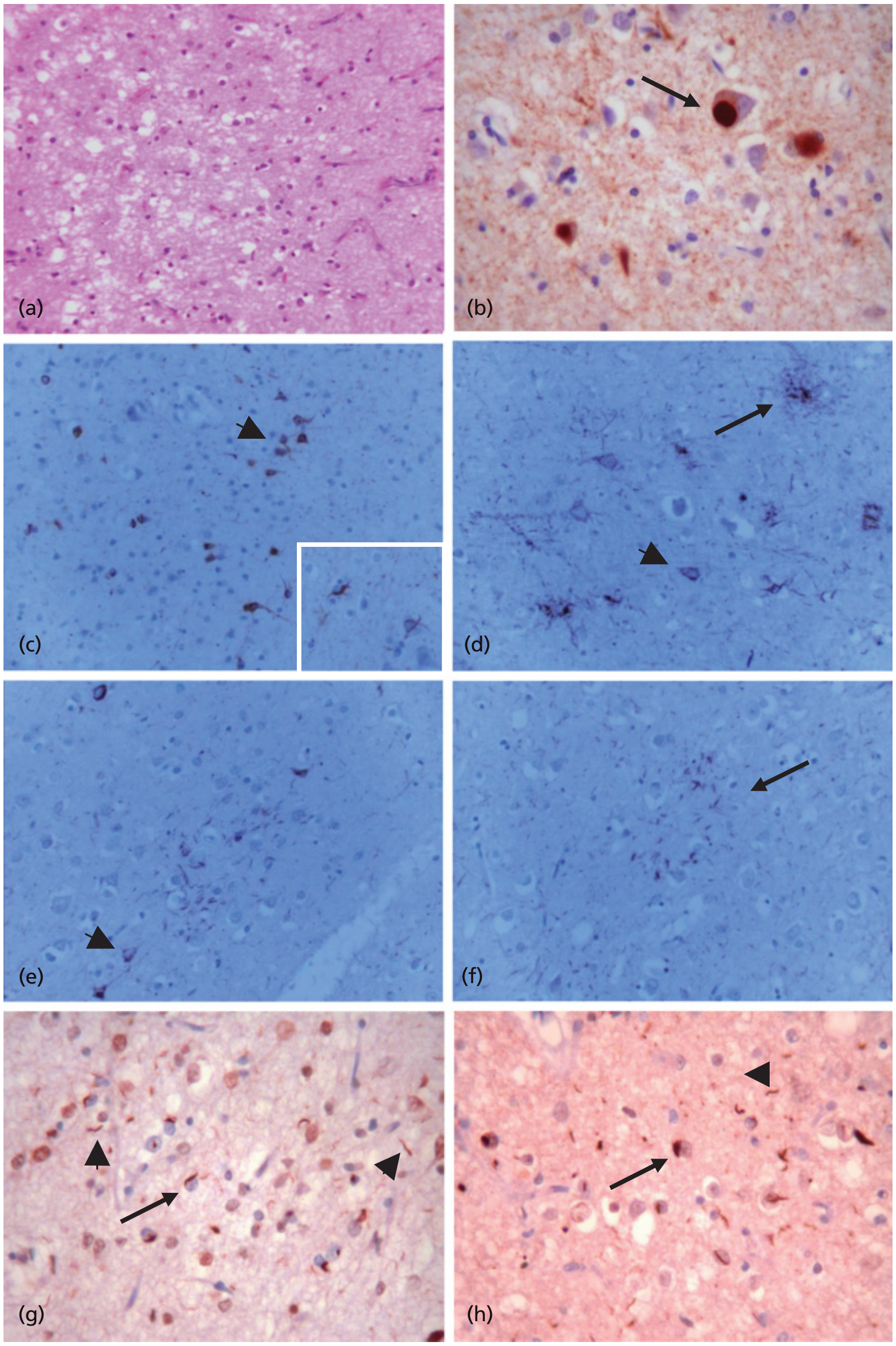


Plate 7.1 (a) Neuropil spongiosis occurring in superficial cortical laminae is seen in FLTD (Haematoxylin and eosin preparation, frontal cortex). (b) Tau-positive Pick body is a characteristic feature of Pick's disease (AT8 immunohistochemistry, temporal cortex). (c) A combination of tau-positive neuronal (arrowhead) and glial pathology is found in FLTD due to intronic mutations located close to the alternatively spliced exon 10 (this case: exon 10 +16 mutation). Insert showing tau-positive oligodendroglial coiled bodies (AT8 immunohistochemistry, temporal cortex). Tau-positive neurofibrillary tangles and pretangles (arrowhead) occur both in progressive supranuclear palsy and corticobasal degeneration (d and e arrowhead). However, tufted astrocytes are the characteristic glial pathology in progressive supranuclear palsy (d arrow) and the so called astrocytic plaques are found in corticobasal degeneration (f arrow) (AT8 immunohistochemistry, frontal cortex). Neuronal intracytoplasmic inclusions (arrow) and neurites (arrowhead) are ubiquitin-positive (g) and are immunoreactive for TDP-43 (h) in FTLD-U (g: ubiquitin immunohistochemistry; h: TDP-43 immunohistochemistry, temporal cortex). Figures courtesy of Professor Tamas Revesz, Queen Square Brain Bank, Department of Molecular Neuroscience, UCL Institute of Neurology.

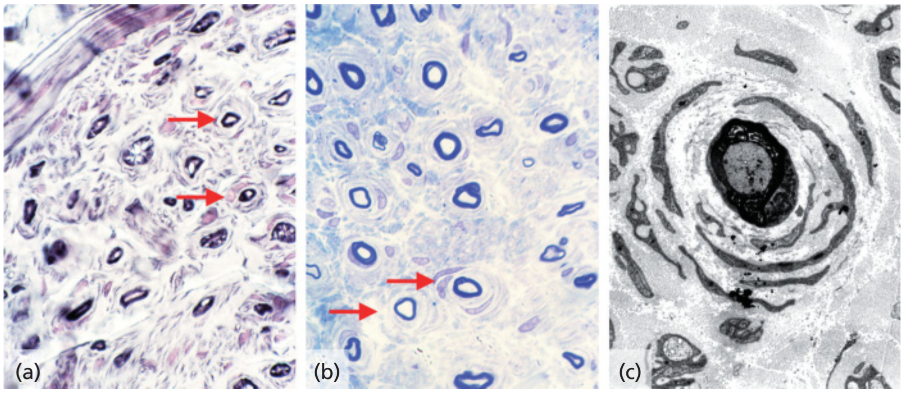


Plate 9.1 Charcot–Marie–Tooth type 1a with formation of onion bulbs. (a) Paraffin section (transverse) shows concentric formations (arrows) with a reduction of fibre density. The interstitial space is widened, indicating oedema with a mucoid component. (b) Semi-thin resin section (toluidine blue) confirms the abundant presence of onion bulbs (arrows). (c) Electron microscopy of the same nerve with concentric arrangement of Schwann cells around myelinated axons. The Schwann cells appear as plump, elongated and rounded stacks, separated by longitudinally oriented collagen fibres (light grey).

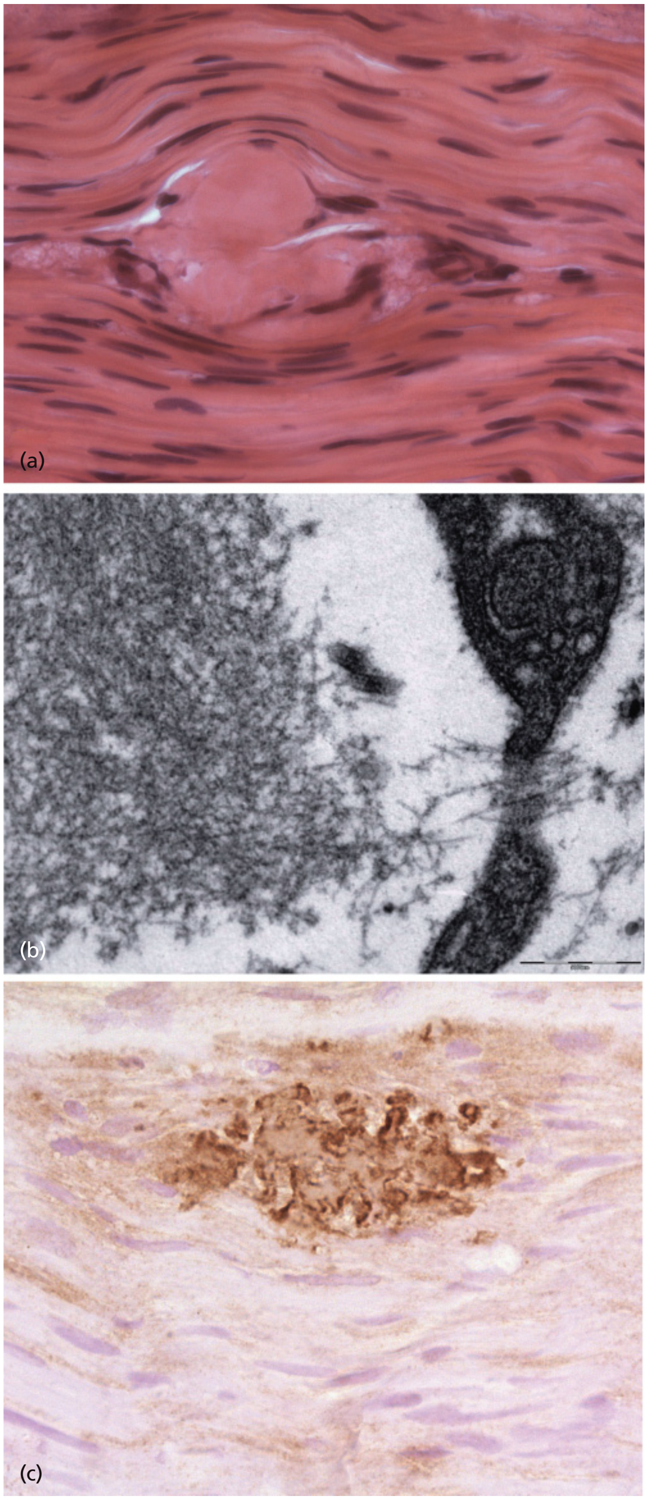


Plate 9.2 Amyloid neuropathy. (a) Haematoxylin and eosin stained paraffin section with a large amyloid deposition in the endoneurium, displacing normal structures. The nerve is severely depleted of large myelinated axons. (b) Electron microscopy of the same nerve, visualizing amyloid fibrils. (c) The amyloid is composed of transthyretin (determined by immunohistochemistry).

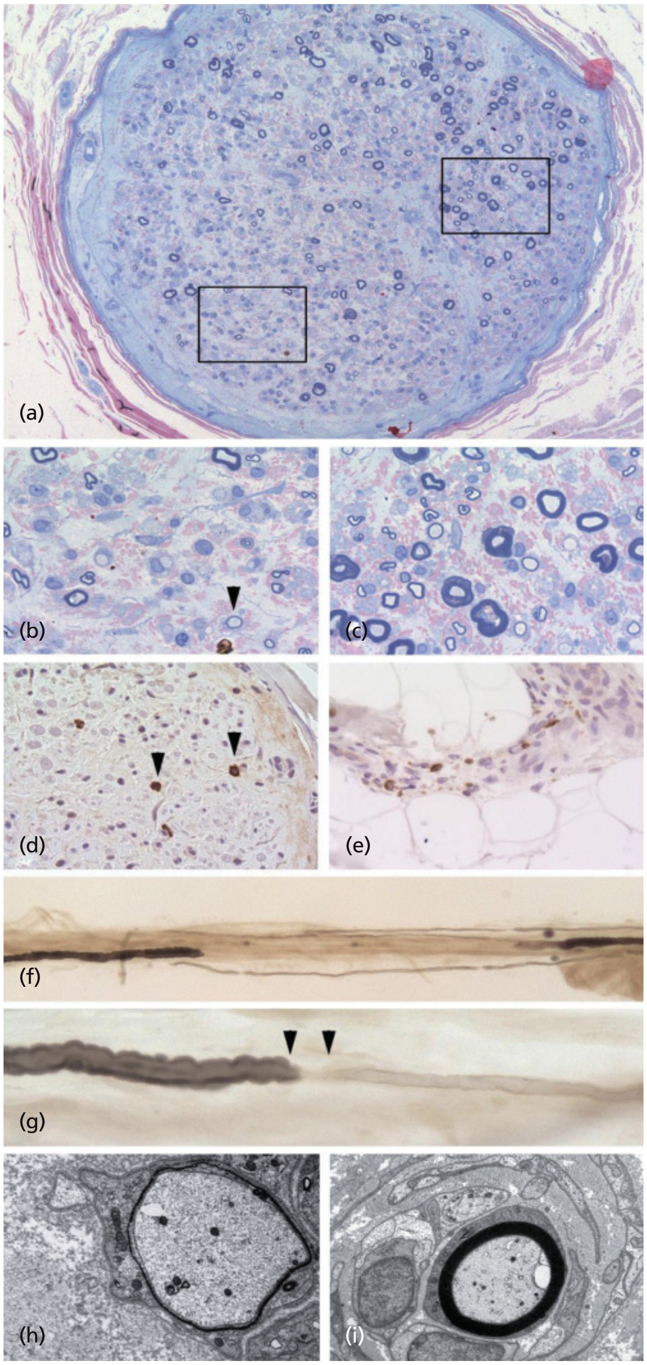


Plate 9.3 Chronic inflammatory demyelinating polyradiculoneuropathy. (a) Patchy loss of myelinated fibres in a fascicle of the sural nerve (semi-thin resin section, toluidine blue). The left lower rectangle is shown in higher magnification in (b). (b) Close-up of the area with a significant loss of large myelinated fibres (arrowhead indicates a thinly myelinated fibre). There are several other thinly myelinated and entirely demyelinated fibres. (c) More densely populated area corresponding to the right upper rectangle in (a). (d) Endoneurial T cells (CD8 immunohistochemical staining). (e) Most CIDPs are also characterized by a variable peri-vascular infiltrate as shown here (CD8 immunohistochemistry). (f) Teased fibre preparation which shows a segmental demyelination. To unequivocally identify segmental demyelination, myelinated fibres have to be identified on either end of the demyelinated stretch. (g) Close-up of demyelination, which shows a myelinated segment on the left, the end of which is indicated by the left arrowhead. This is followed by an expanded internode length, the end of which is indicated by the right arrowhead. The subsequent stretch of the axon is very thinly myelinated. (h) Electron microscopy of a demyelinated and thinly remyelinated axon. (i) Axon with almost regular myelin thickness, surrounded by concentric formations of Schwann cell laminae, also designated onion bulbs.

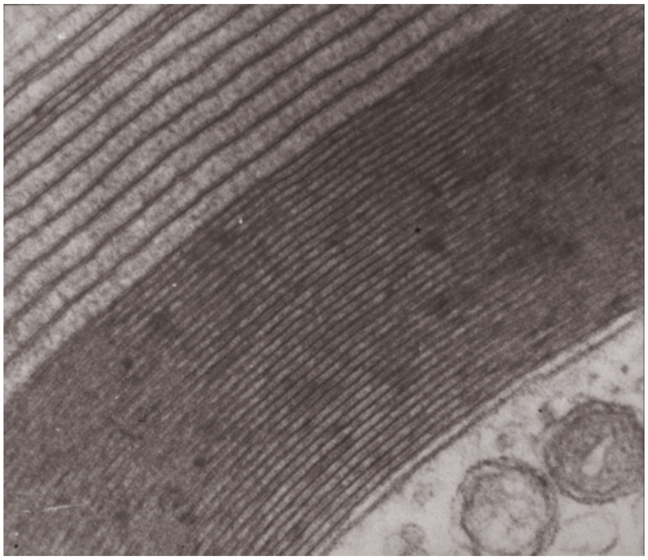


Plate 9.4 Widely spaced myelin. The normal myelin lamellae are tightly compacted and have a periodicity in electron microscope preparations of 12–15 nm. In the demyelinating neuropathy associated with immunoglobulin M (IgM) paraprotein that has activity against MAG (anti-Mag PDPN) the intraperiod line becomes split giving an overall periodicity of 30–40 nm. There is a suggestion of material within the widened spaces, possibly IgM.

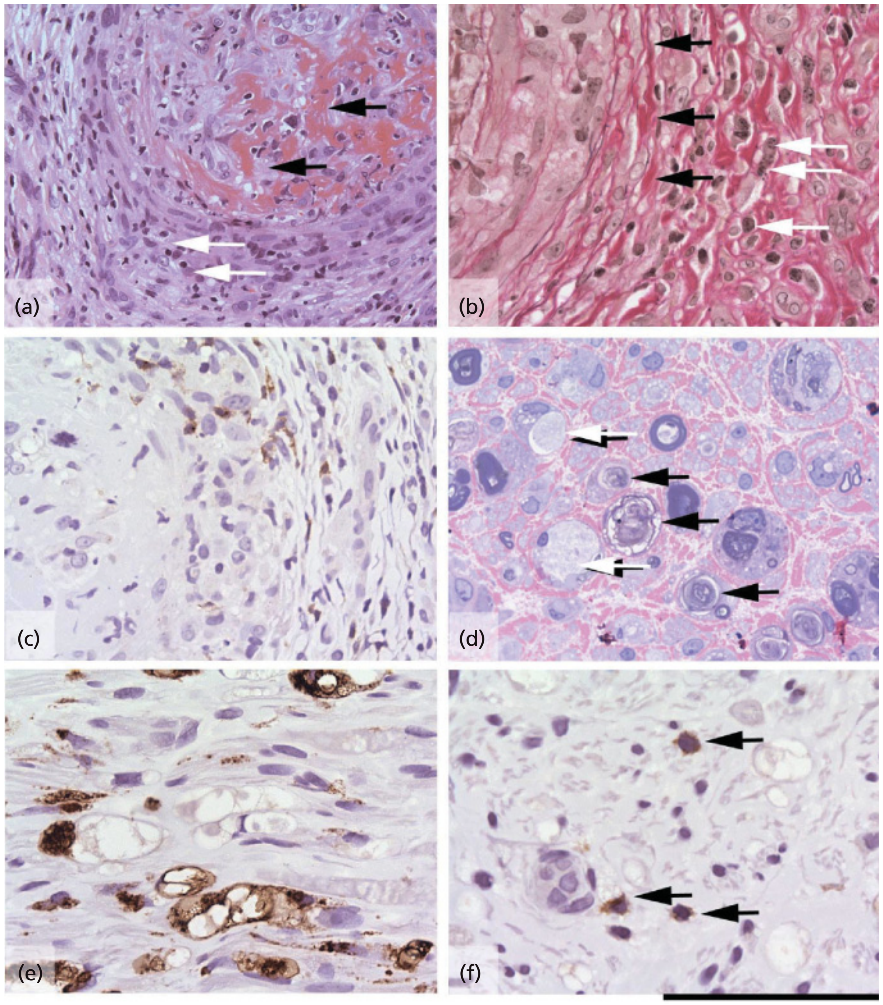


Plate 9.5 Vasculitis and severe axonal neuropathy in a peripheral nerve. (a) Fibrinoid necrosis (black arrow) of a medium-sized vessel. The vessel wall is densely infiltrated by inflammatory cells (white arrows). (b) Van Gieson elastica staining to visualize the distended and infiltrated vessel walls (red, black arrows) and interdispersed lymphocytes (white arrows). (c) CD8 immunohistochemical staining to visualize T cells in the vessel walls. (d) Semi-thin resin sections on a transverse section of the adjacent nerve. Black arrows show acutely degenerating axons. White arrows indicate macrophages with the characteristic fine granular bright cytoplasm and peripheral small dark nucleus. (e) CD68 immunohistochemical staining to visualize digestion chambers and macrophage in the acutely degenerating nerve. (f) Accompanying occasional T-cell infiltrates in the affected nerve. This is regarded as a bystander effect to the overall inflammatory disease and should not be regarded as primary inflammation.

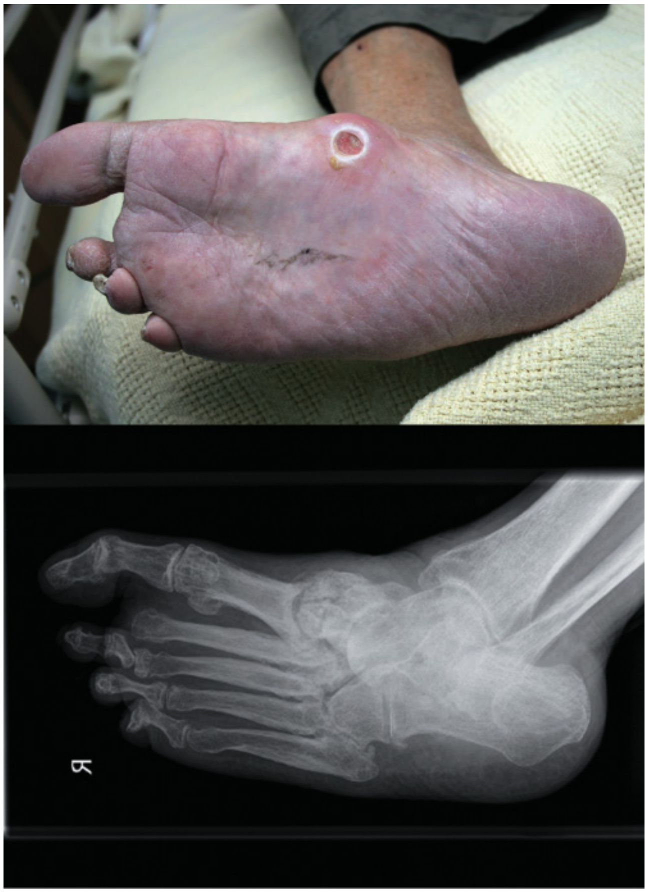


Plate 9.6 Charcot joint in a foot secondary to recurrent severe vasculitic neuropathy. The second phalanx has been amputated and a new vasculitic ulcer is present on the sole of the foot.

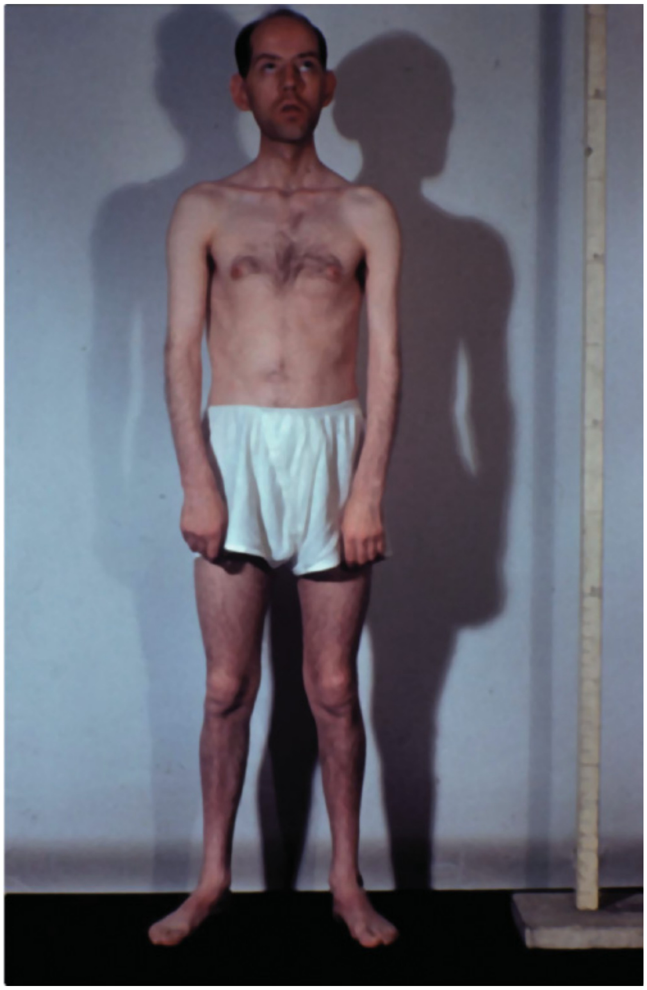


Plate 9.7 Typical clinical appearance of a patient with myotonic dystrophy. Note ptosis, frontal balding, typical facies and distal wasting.

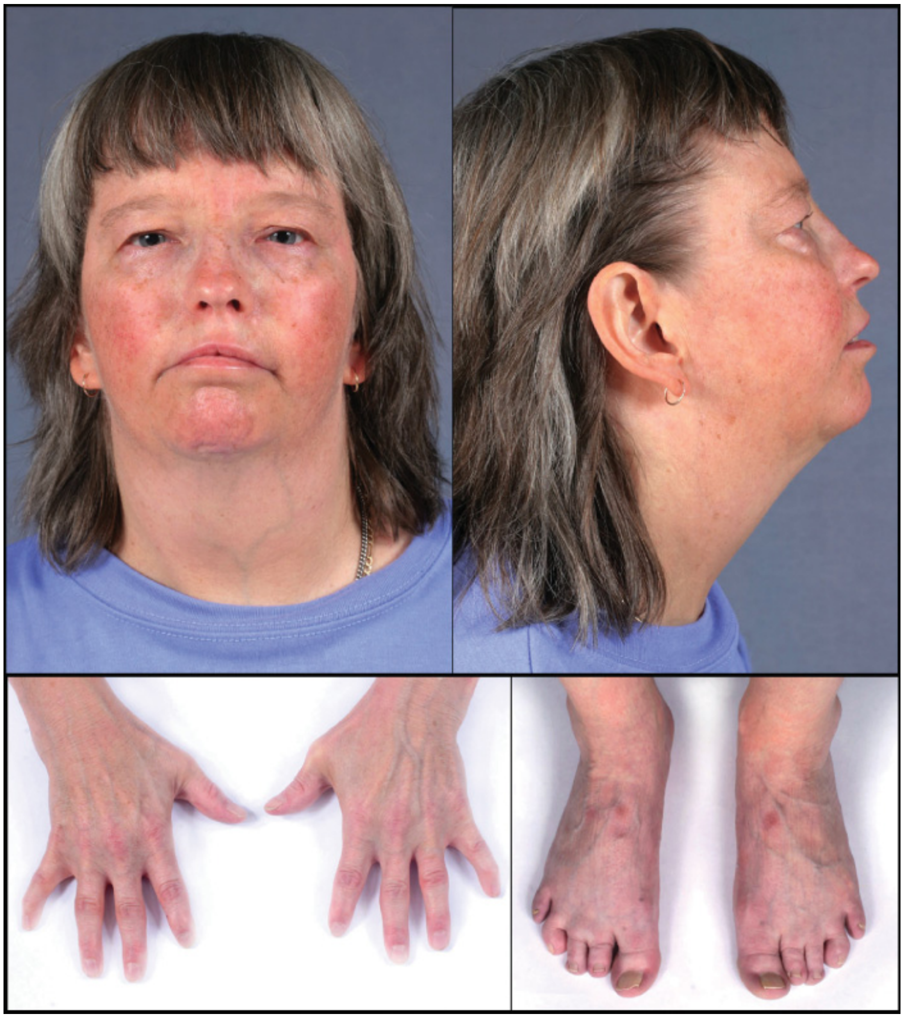


Plate 9.8 Typical facial, hand and foot appearances in Anderson–Tawil syndrome. Note hypertension, micrognathism, low-set ears, down-turned mouth, short digits, clinodactyly of the fifth digits and syndactyly of the toes.

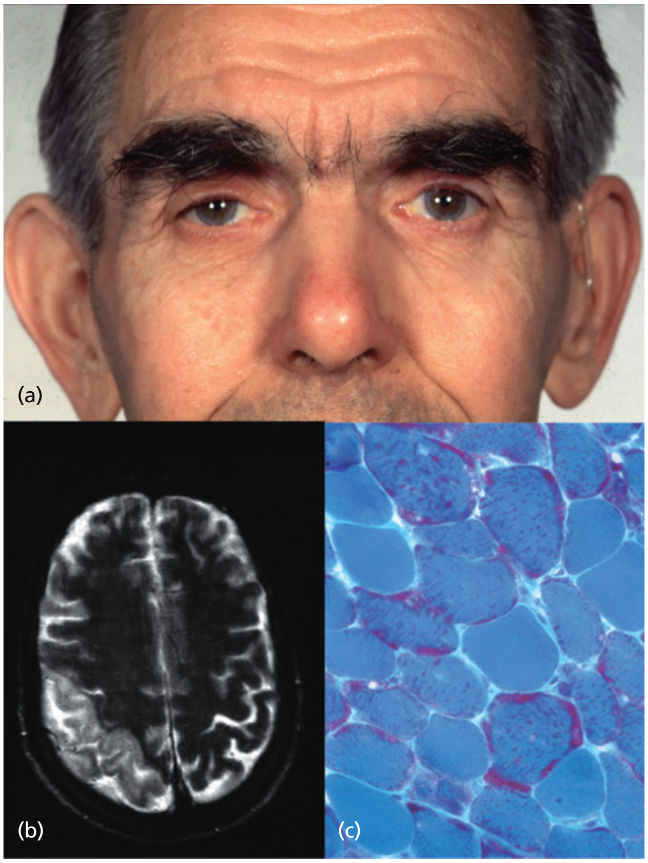


Plate 9.9 (a) Mitochondrial myopathy. Note not only the ptosis but hearing aid indicating deafness. (b) MRI T2W showing occipito-parietal, not respecting usual anotomical vascular territories, following a stroke-like episode in a case of mitochondrial disease. (c) Ragged red fibres stained with Gomori Trichrome stain – muscle fibres with peripheral accumulations of abnormal mitochondria.

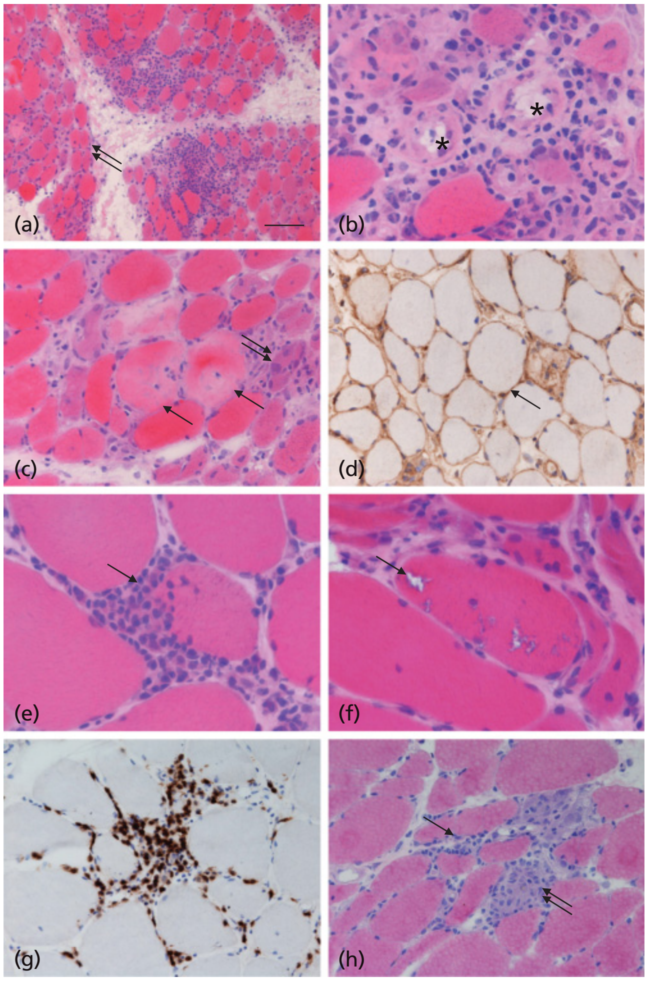


Plate 9.10 In dermatomyositis, atrophic fibres often display a peri-fascicular arrangement (a, double arrow). Lymphocytic infiltrates are frequently peri-vascular (b, * indicate small arterioles) and peri-mysial but may extend into the endomysium. There is fibre necrosis (c, arrows) and regeneration (c, double arrow). MHC Class I is expressed at the sarcolemma (d, arrow). The features of inclusion body myositis include endomysial lymphocytic infiltration with infiltration into intact muscle fibres (e, arrow) and rimmed vacuoles that occur in fibres without lymphocytic infiltration (f, arrow). The inflammatory infiltrate is composed predominantly of CD8-positive T lymphocytes (g). In polymyositis, the inflammation is largely endomysial in location (h, arrow). In this example, necrotic fibres infiltrated by macrophages are prominent (h, double arrow). a–c, e, f, h, haematoxylin and eosin; d, immunohistochemical staining for MHC Class I; g, immunohistochemical staining for CD8.

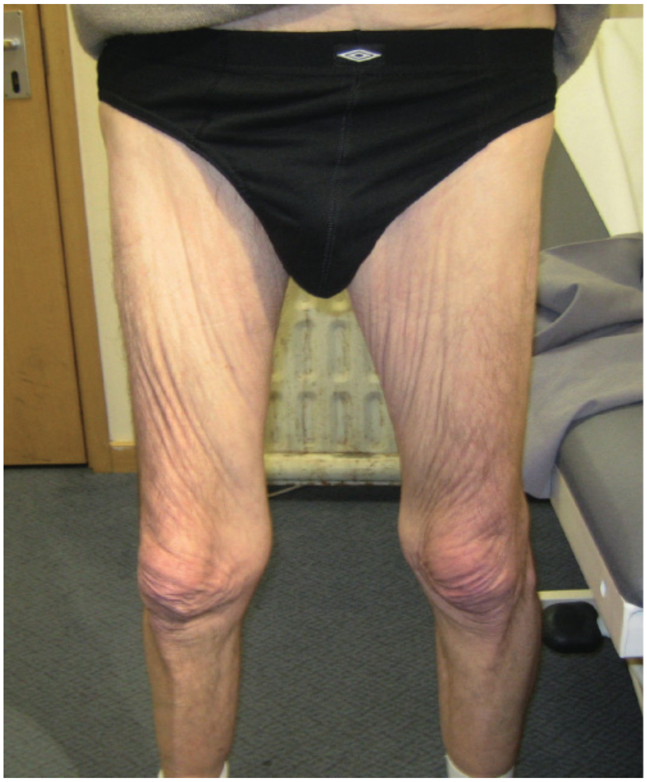


Plate 9.11 Inclusion body myositis may present with focal weakness of the quadriceps muscles, identified easily in this case by the focal thigh wasting – when compared to the lower leg muscle compartments.

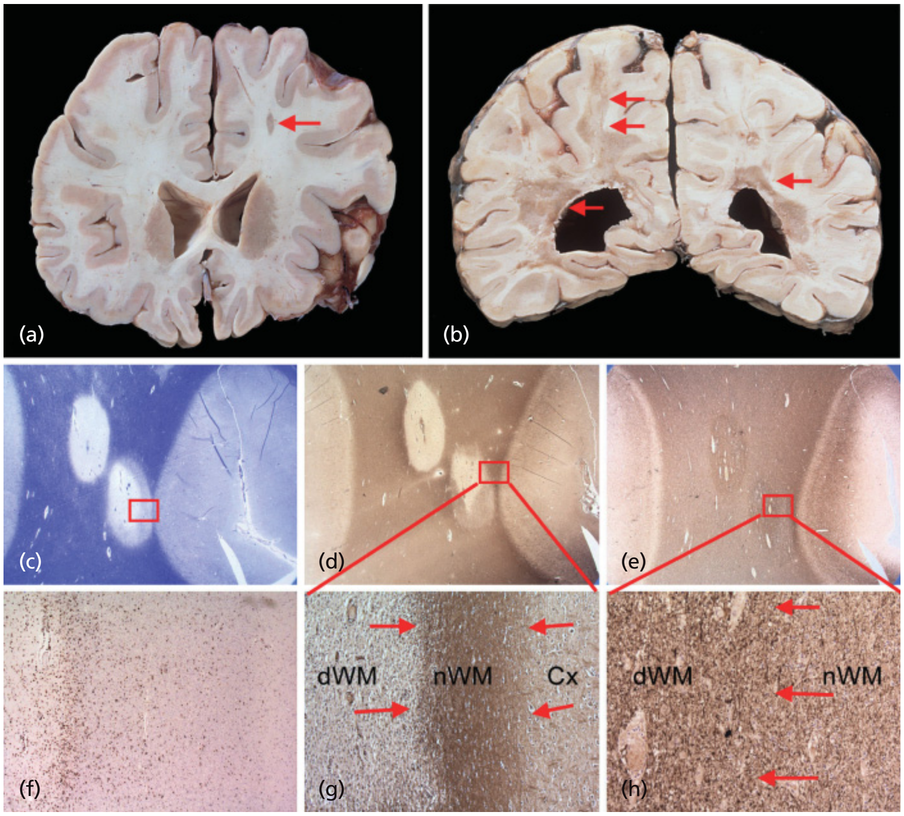


Plate 10.1 Macroscopic and microscopic findings in multiple sclerosis. (a,b) Macroscopic pathology of demyelination (coronal sections of formalin fixed brains). (a) Arrow pointing at a small circumscribed demyelination in the frontal white matter. Loss of myelin appears grey, similar to cerebral cortex. (b) Coronal section of the occipital lobe with extensive multi-focal and confluent demyelinations (arrowhead). (c–e) Two foci of demyelination, one with partial remyelination (red box) stained for myelin or axons. (c) Luxol fast blue stains myelinated structures dark blue and the punched-out well-demarkated defects indicates loss of myelin. (d) Myelin basic product (MBP) immunohistochemistry labels myelinated fibres, and shows the same punched-out demyelination with a smaller rim of remyelination fibres in the lowest lesion. (e) Immunohistochemical staining of phosphorylated neurofilament demonstrates the prescence of axons within the demyelinating lesions, which appear of slightly increased density than the surrounding intact white matter. (f) CD68 immunohistochemistry labels microglia and macrophage activity. The area corresponds to the red rectangle in (c–e), it clearly shows a demarcation between demyelinated and remyelinated regions. (g) High power magnification of the boxed area in (d) (MBP) on the left with loss of the myelin (demyelinated white matter [dWM]), a myelinated area in the centre (WM) and normal cortex (Cx) with myelinated on the right, all indicated by arrows. (h) High magnification of the labelled area in (e) shows the axons in the lesion on the left (dWM) and outside the lesion (nWM), the border is indicated by arrows. (Images and macroscopic specimens courtesy of Sebastian Brandner; histological specimens courtesy of Klaus Schierer, UCL Institute of Neurology.)

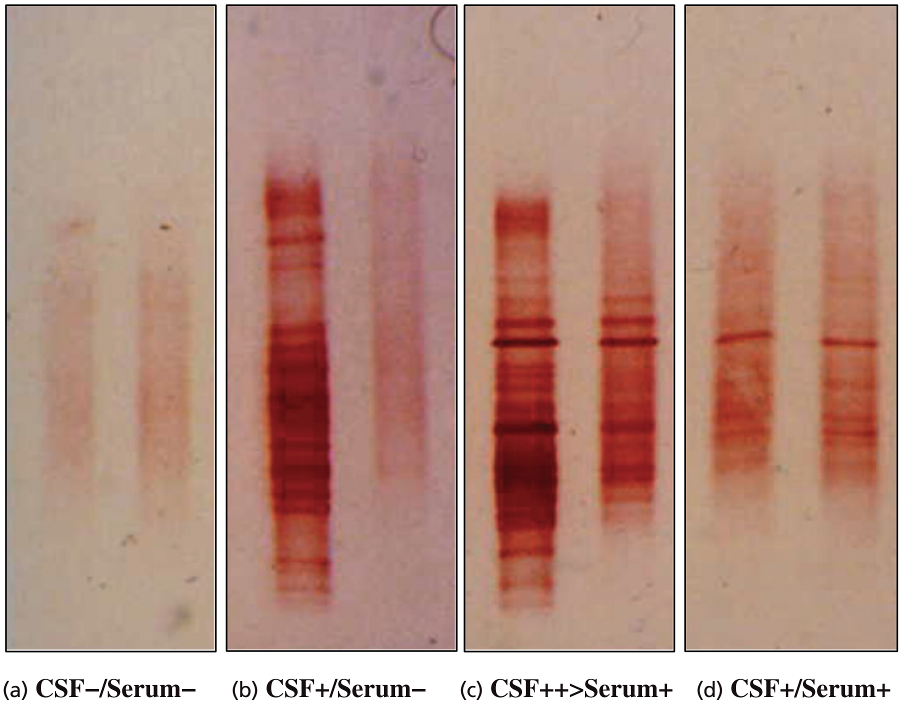

(a) CSF−/Serum−
(b) CSF+/Serum−
(c) CSF++>Serum+
(d) CSF+/Serum+

Plate 10.2 Isoelectric focusing of paired cerebrospinal fluid (CSF) and serum. (a) CSF–/serum–. (b) CSF+/serum–. (c) CSF++/serum+. (d) CSF+/serum+. The oligoclonal band patterns in (b) and (c) indicate intrathecal antibody synthesis.

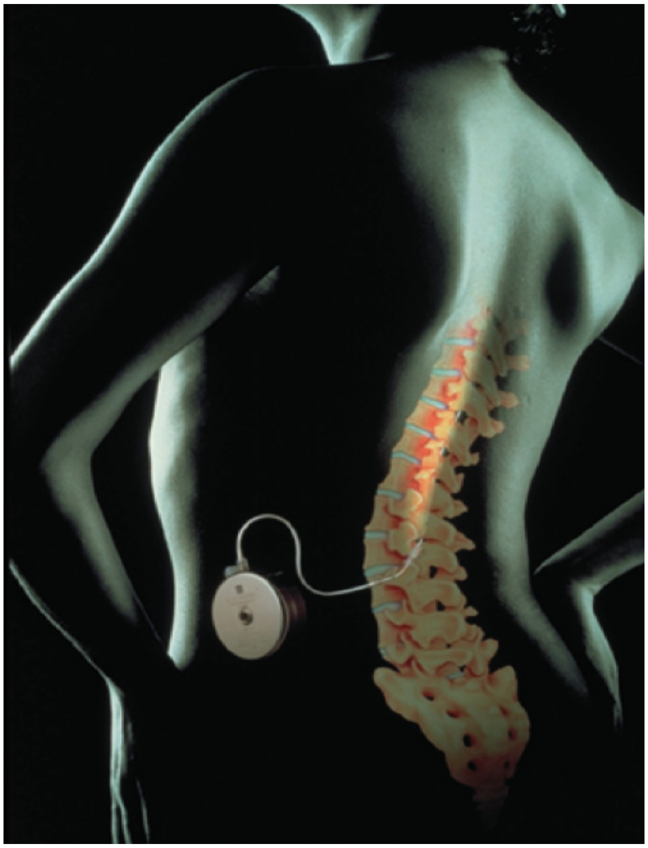


Plate 10.3 Abdominally placed baclofen pump and intrathecal catheter. Medtronic™.

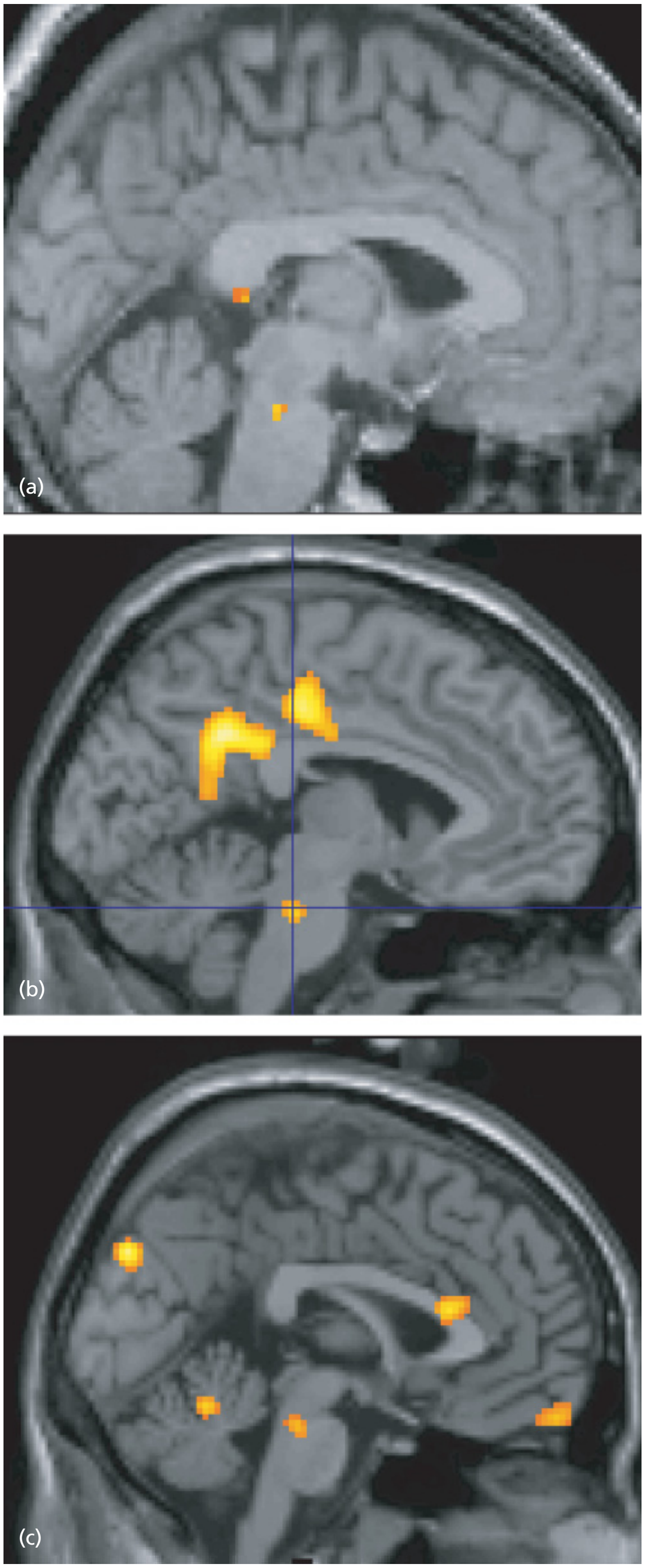


Plate 11.1 Activation on positron emission tomography (PET) in a patient with cluster headache and migraine (a) who experienced a migraine without aura during the scan after nitrate triggering, and demonstrated activation in the rostral ventral pons. Similarly activation in the same region with spontaneous attacks of episodic migraine (b) and in chronic migraine (c).

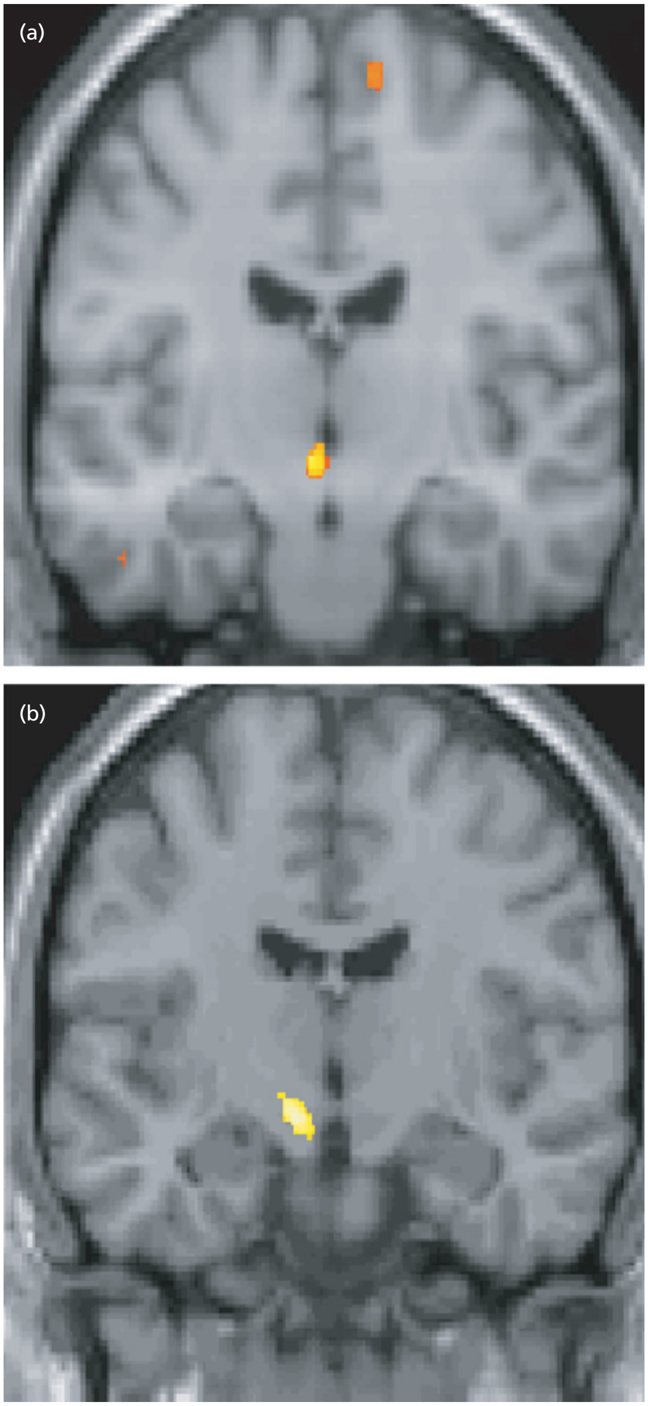


Plate 11.2 Activation on positron emission tomography (PET) in the posterior hypothalamic grey matter in patients with acute cluster headache (a). The activation demonstrated is lateralized to the side of the pain (May *et al.* 1998). When comparing the brains of patients with cluster headache with a control population using an automatic anatomical technique known as voxel-based morphometry (VBM) that employs high-resolution T1-weighted MRI, a similar region is shown (b) with increased grey matter signal activation (May *et al.* 1999).

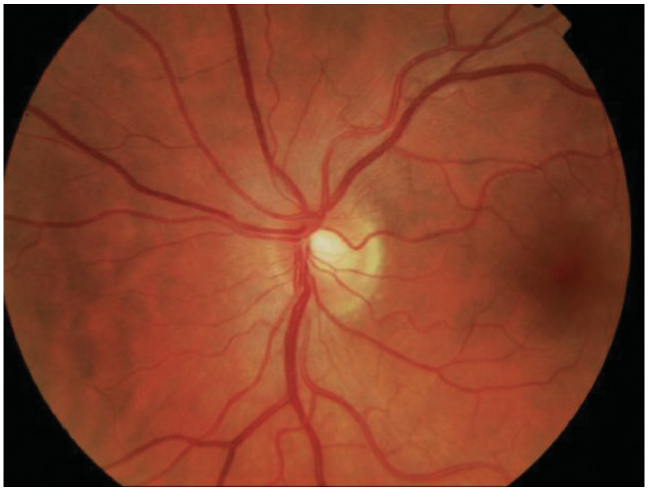


Plate 13.1 Mild optic disc swelling in acute demyelinating optic neuritis. The absence of haemorrhages or exudates is characteristic.

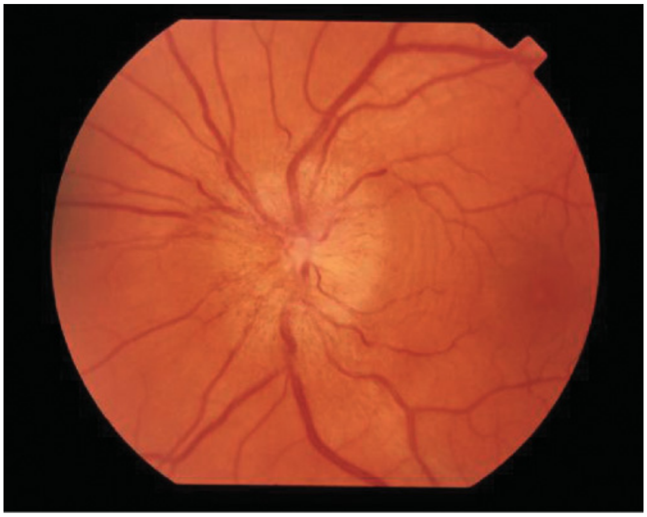


Plate 13.2 Optic neuritis in secondary syphilis. Typically, slit lamp examination shows vitreous cells.

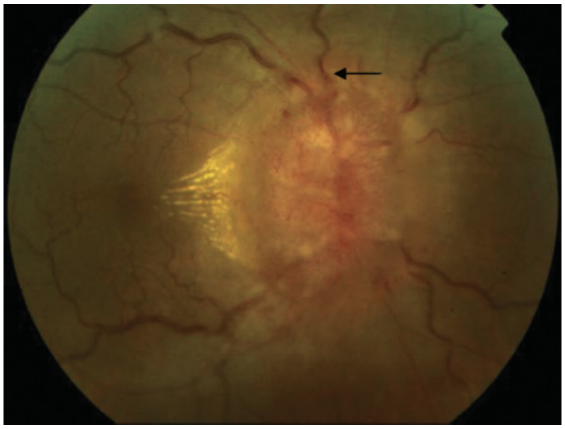


Plate 13.3 Acute neuroretinitis. Note the hard exudates, swollen disc and perivenous infiltrates (arrow).

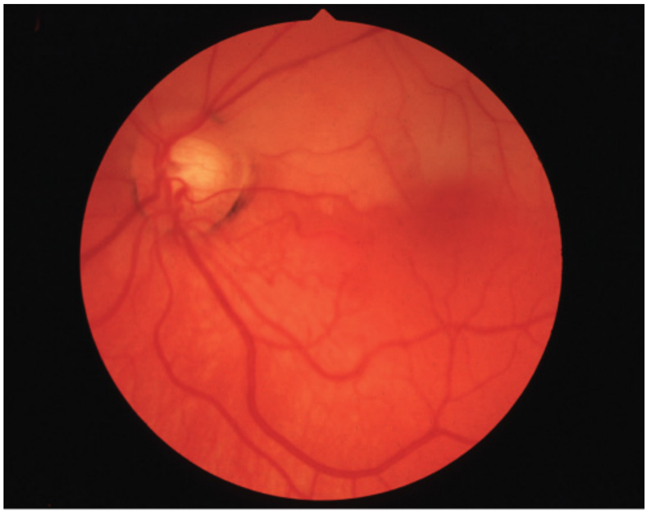


Plate 13.4 Branch retinal artery occlusion. Note the cloudy retinal swelling superiorly.

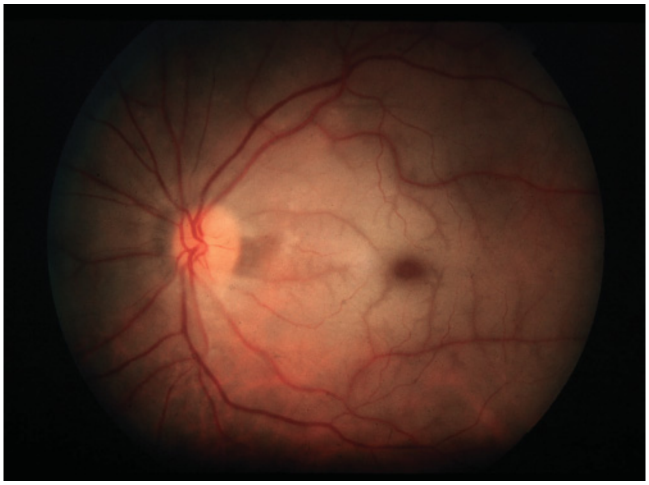


Plate 13.5 Central retinal artery occlusion with cherry red spot.

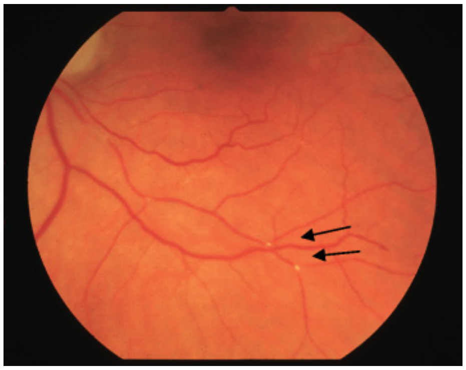


Plate 13.6 Cholesterol emboli (arrows).

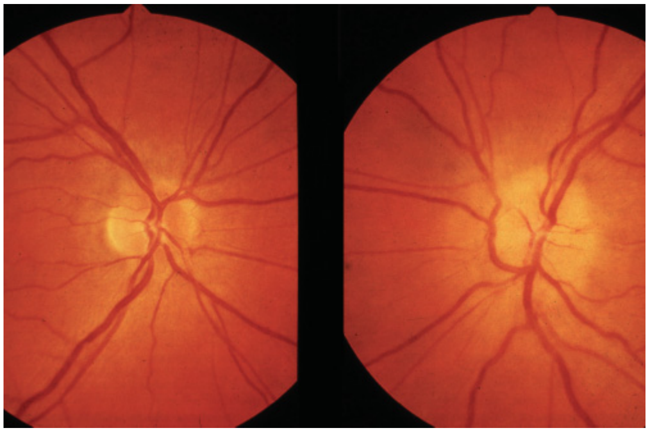


Plate 13.7 Left optic disc swelling and crowded right disc with absent physiological cup in non-arteritic ischaemic optic neuropathy.

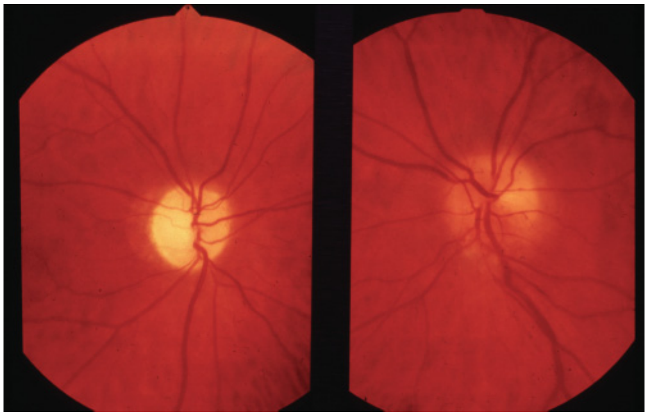


Plate 13.8 Pseudo-Foster Kennedy syndrome. Left optic disc swelling caused by non-arteritic AION; right optic disc atrophy resulting from previous episode.

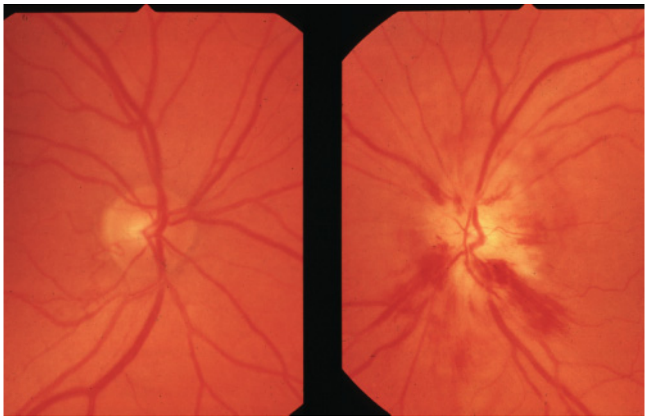


Plate 13.9 Vasculitic anterior ischaemic optic neuropathy (AION) – note left disc swelling with pallor and flame-shaped haemorrhages.

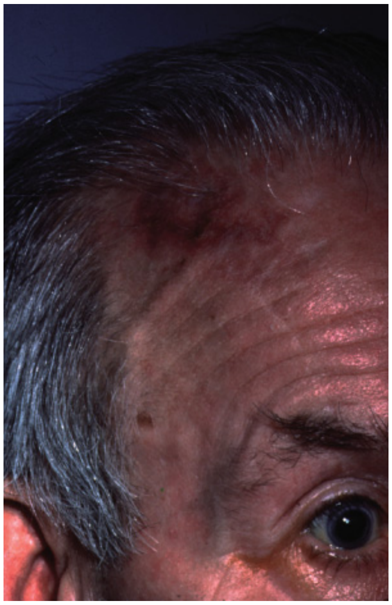


Plate 13.10 Temporal arteritis with superficial scalp necrosis.

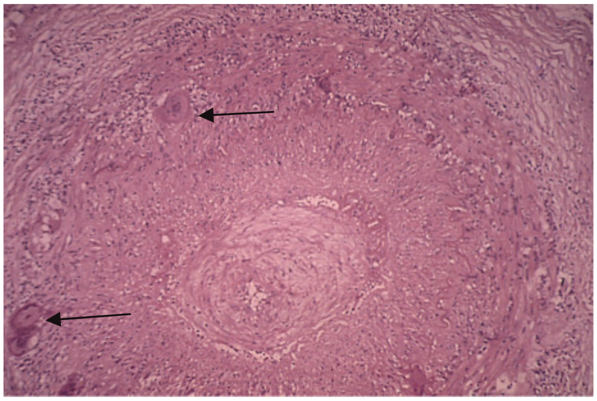


Plate 13.11 Temporal arteritis histology. Note massive intimal thickening to obliterate vascular lumen and multinucleate giant cells (arrows).

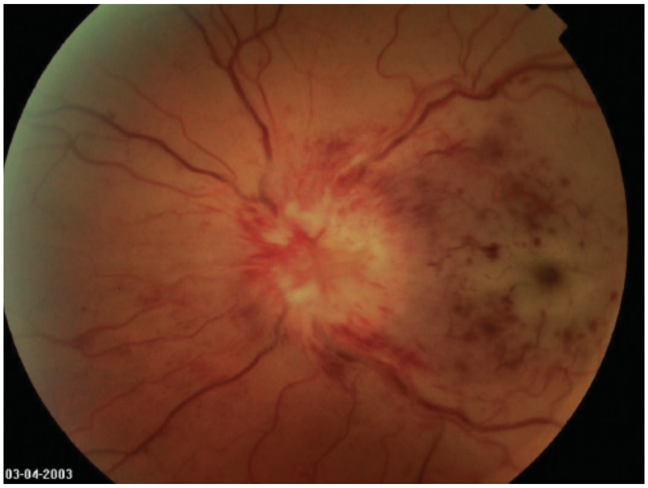


Plate 13.12 Optic disc swelling plus cherry red spot in neoplastic infiltration.

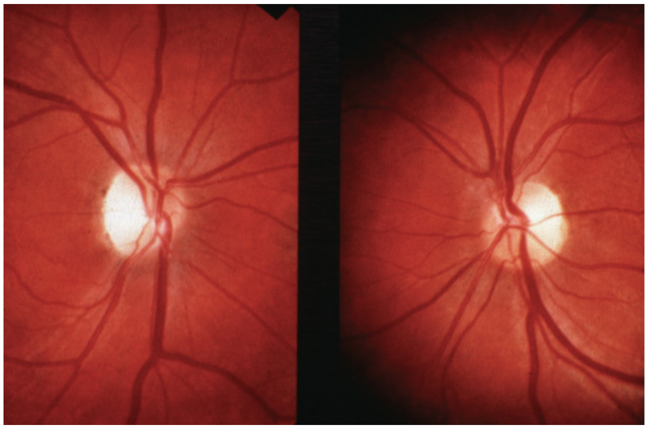


Plate 13.13 Bilateral optic atrophy caused by dominant optic atrophy.

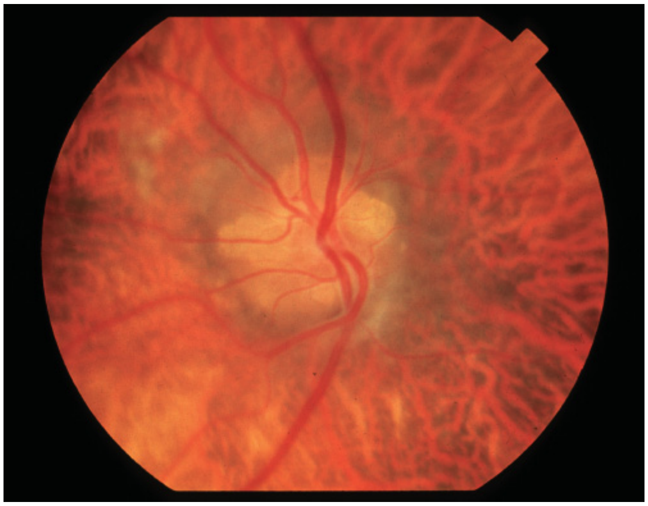


Plate 13.16 Disc drusen. Note anomalous vessel branching and absent physiological cup.

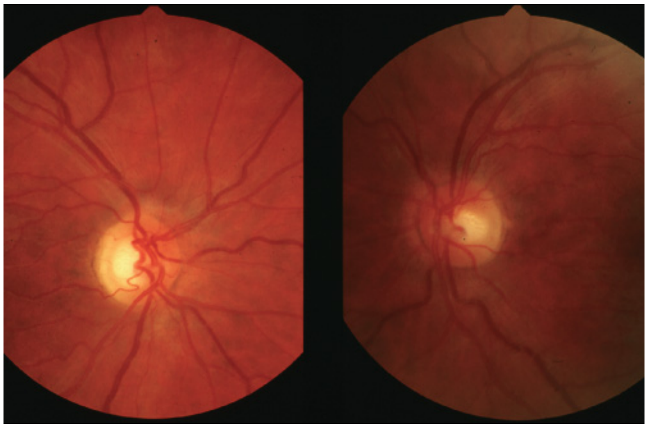


Plate 13.14 Temporal optic disc pallor in established Leber's hereditary optic neuropathy.

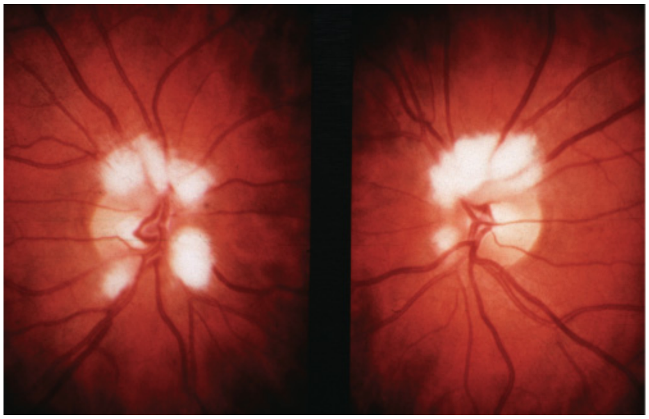


Plate 13.17 Myelinated retinal nerve fibres.

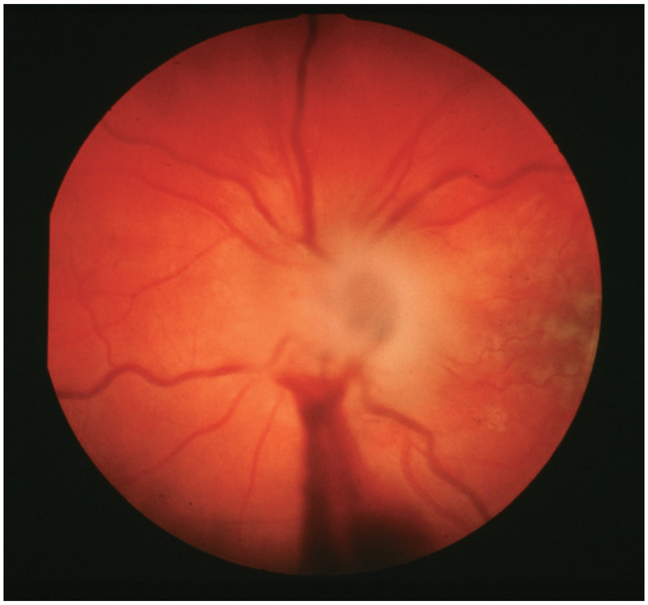


Plate 13.15 Traumatic optic neuropathy.

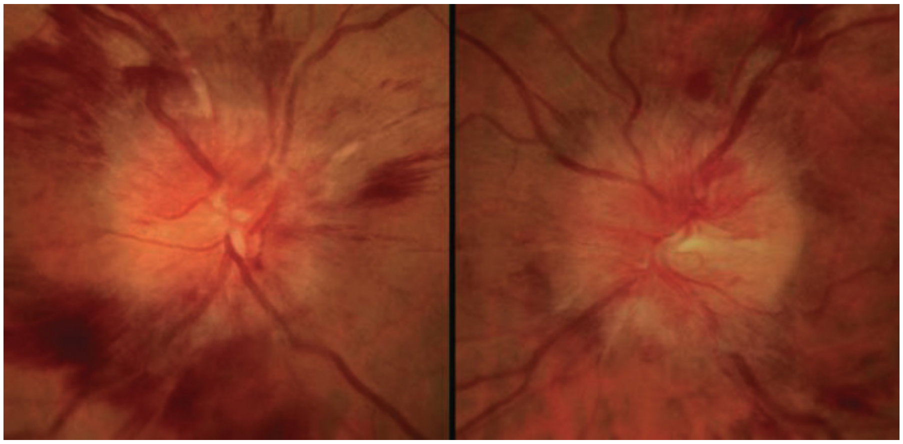


Plate 13.18 Acute haemorrhagic papilloedema.

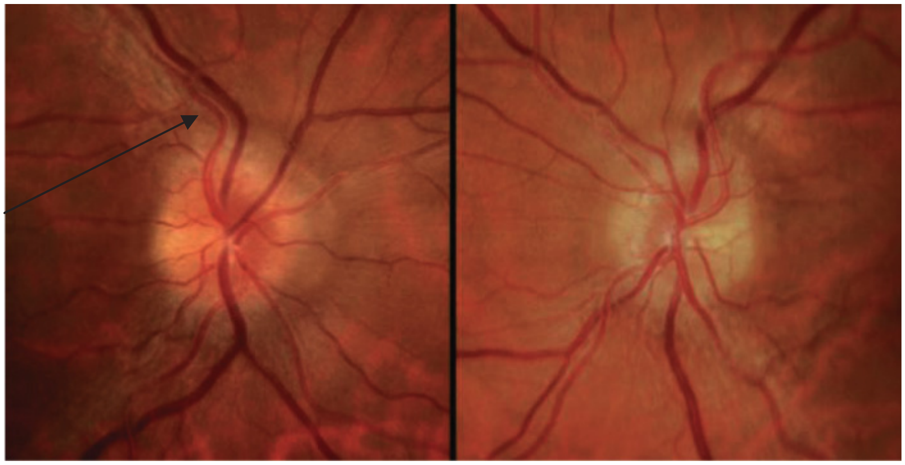


Plate 13.19 Early papilloedema. Note nerve fibre layer swelling starting to obscure right supero-temporal branch retinal artery (arrow).

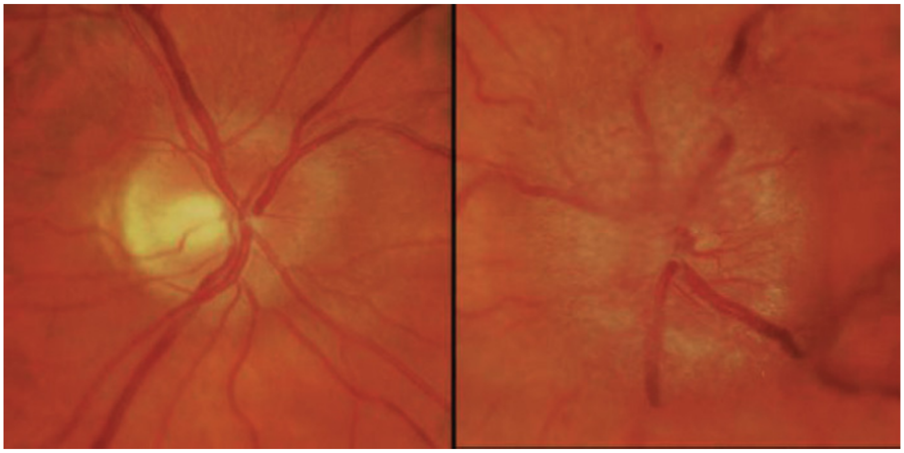


Plate 13.20 Asymmetrical bilateral papilloedema.

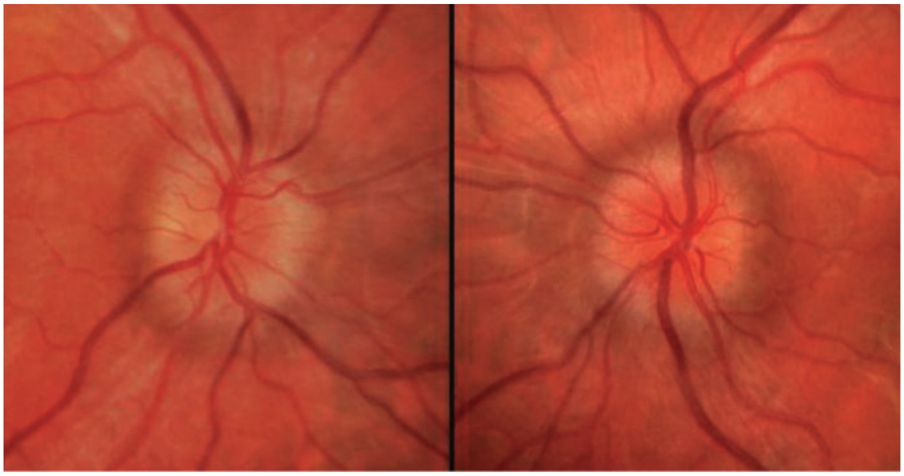


Plate 13.21 Chronic compensated papilloedema.

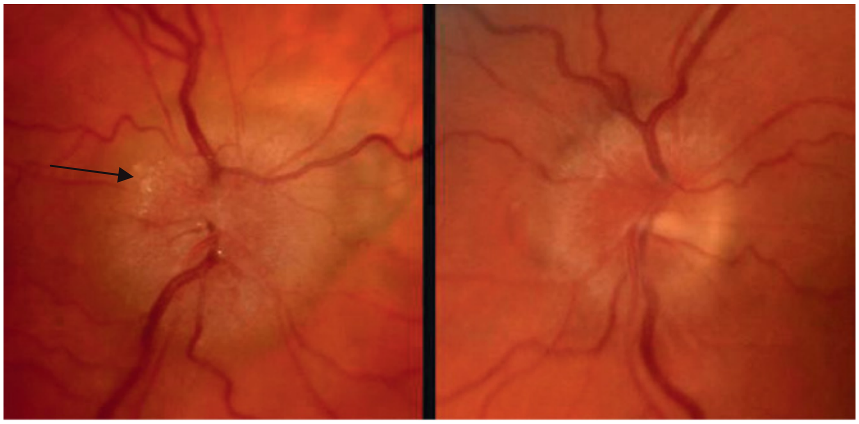


Plate 13.22 Vintage papilloedema with corpora amylacea (arrowed).

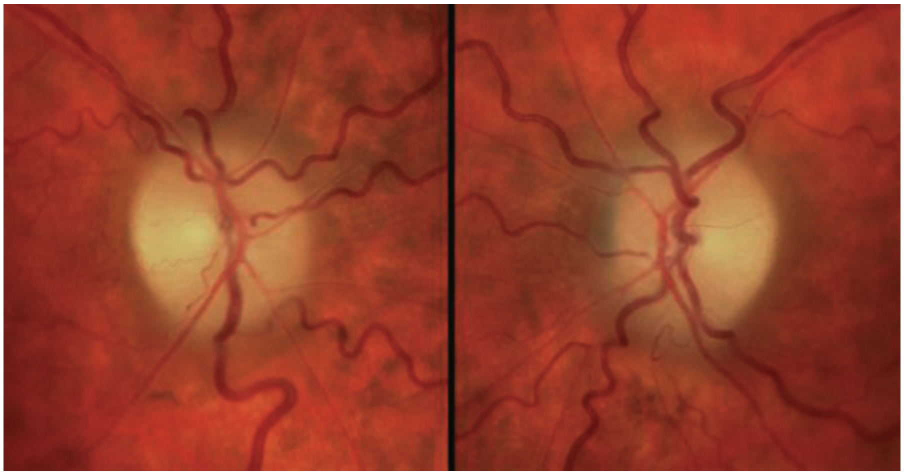


Plate 13.23 Atrophic papilloedema.

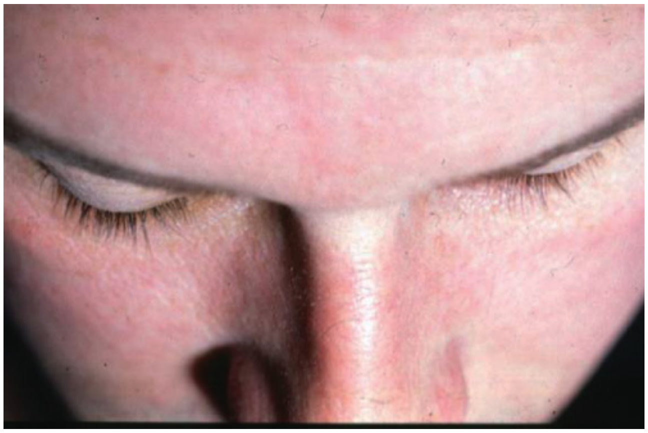


Plate 13.24 Subtle right proptosis due to orbital mass is best observed from above.

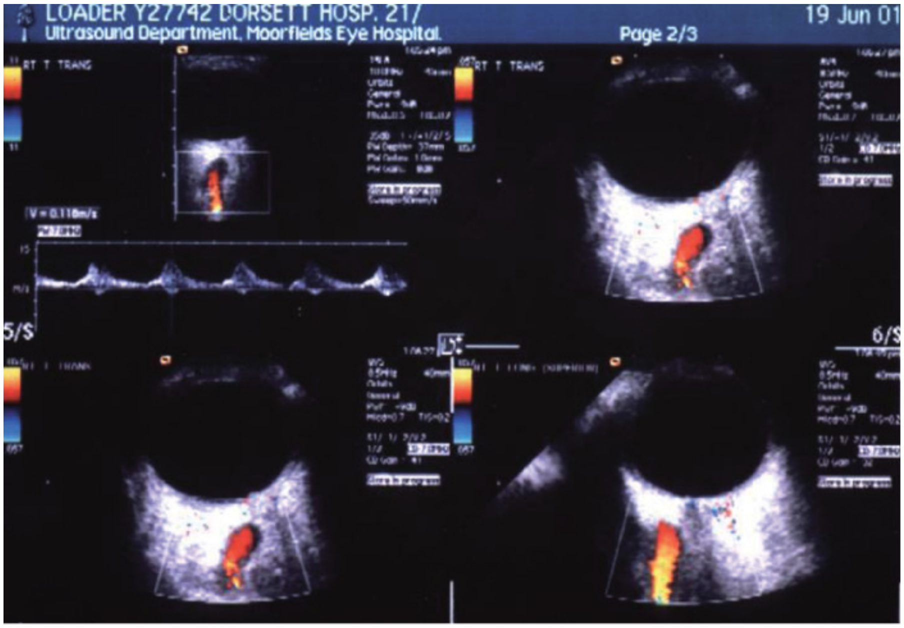

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Plate 13.25 Colour Doppler flow mapping showing flow reversal (red) in superior ophthalmic vein due to carotid-cavernous fistula.

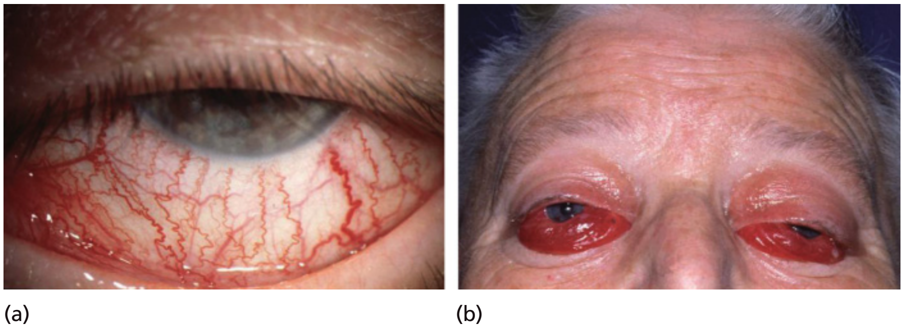


Plate 13.26 (a) Arterialized conjunctival vessels in carotid-cavernous fistula. (b) Bilateral chemosis in carotid-cavernous fistula.

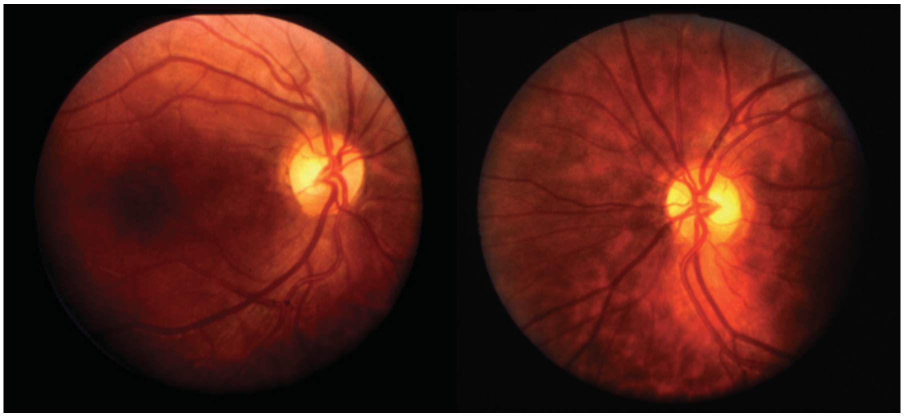


Plate 13.27 Band atrophy in bitemporal hemianopia due to chiasmal transection.

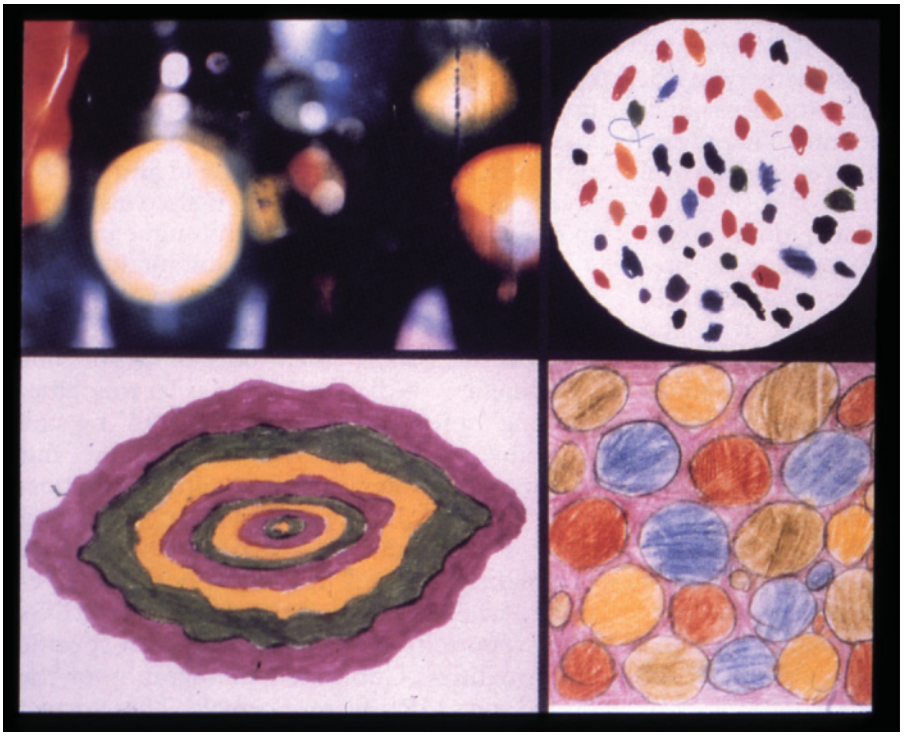


Plate 13.28 Visual phenomena recorded by four patients with occipital epilepsy. (Reproduced from Panyiotopoulos, 1999 with permission.)

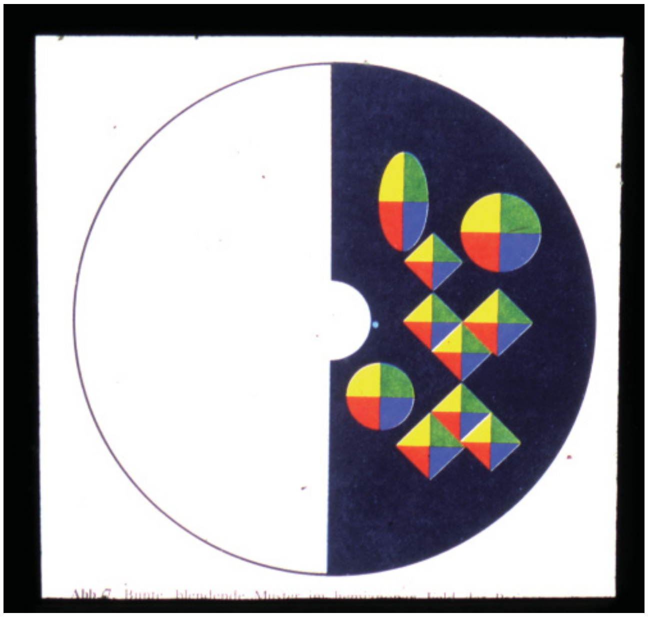


Plate 13.29 Geometric hallucinations within a hemianopic field defect recorded by the patient. (Reproduced from Kölmel, 1985 with permission.)

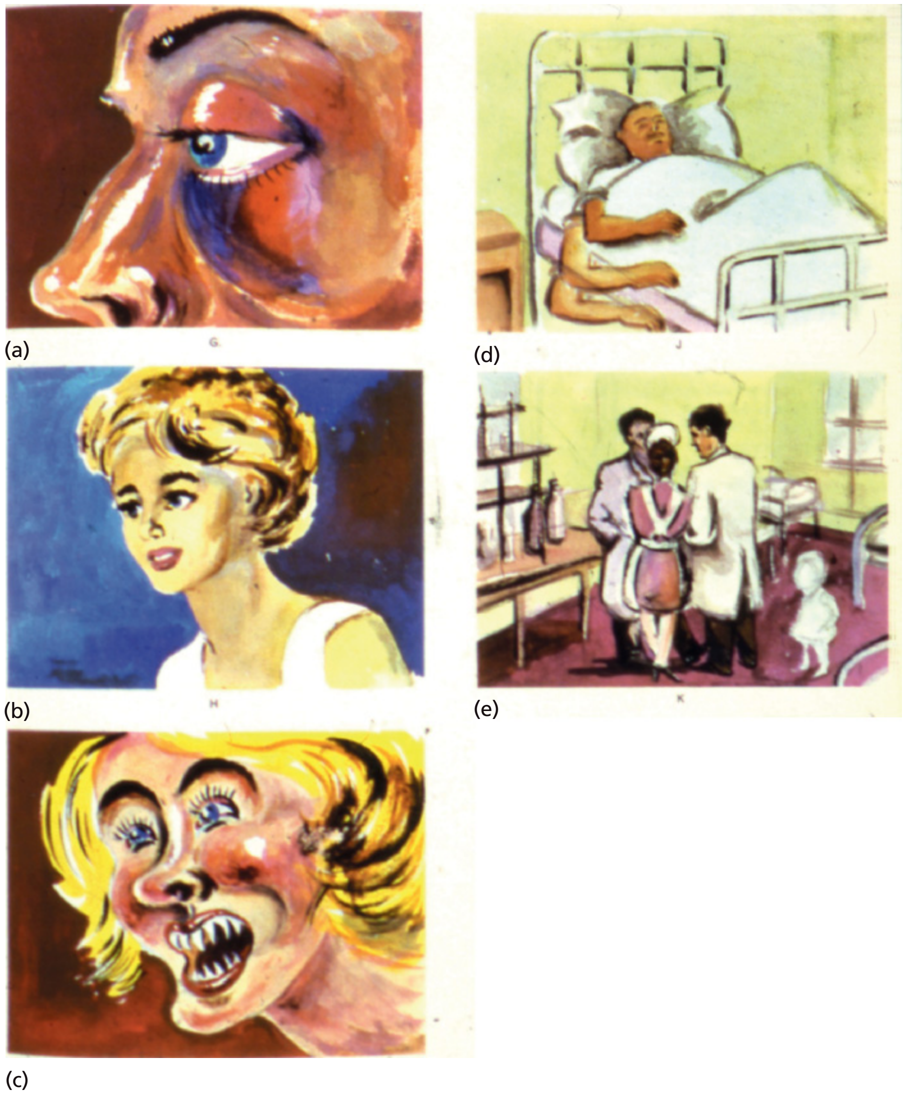


Plate 13.30 Metamorphopsia recorded by a patient following occipital lobe surgery. (From Mooney *et al.* 1965, with permission.)

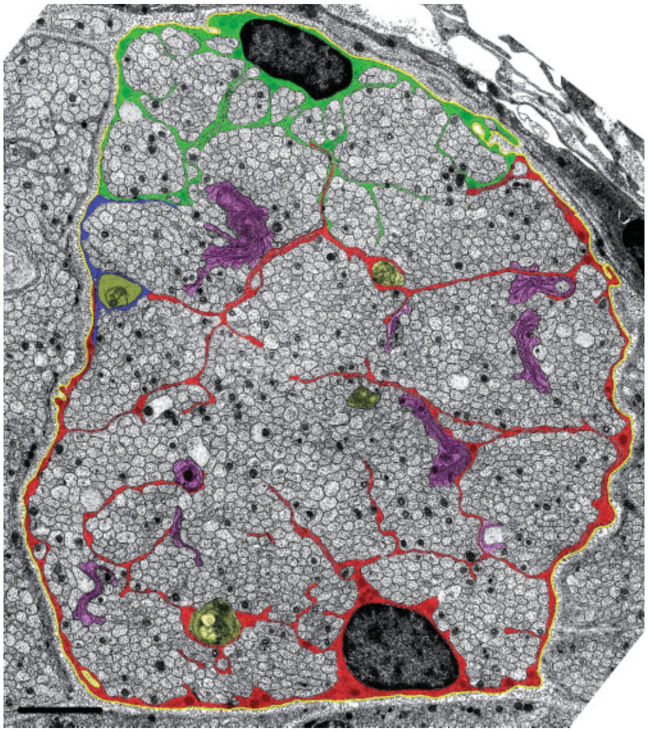


Plate 15.1 Electronmicrograph of olfactory ensheathing cells (OECs). Each colour represents the cytoplasm of a different OEC.

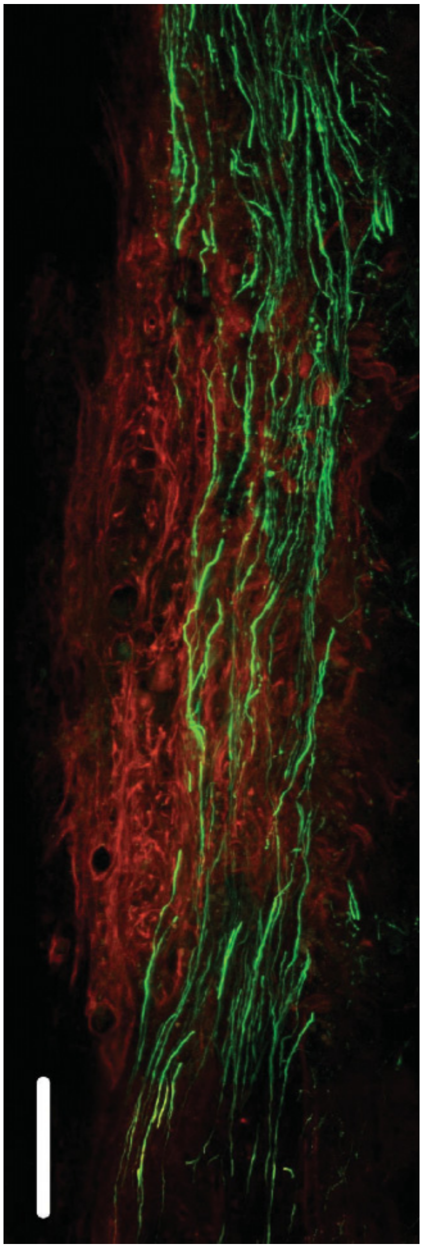


Plate 15.2 Photomicrograph of longitudinal section of rat spinal cord showing regeneration of neurones (green) through an area of transplanted olfactory ensheathing cells (OECs; red).

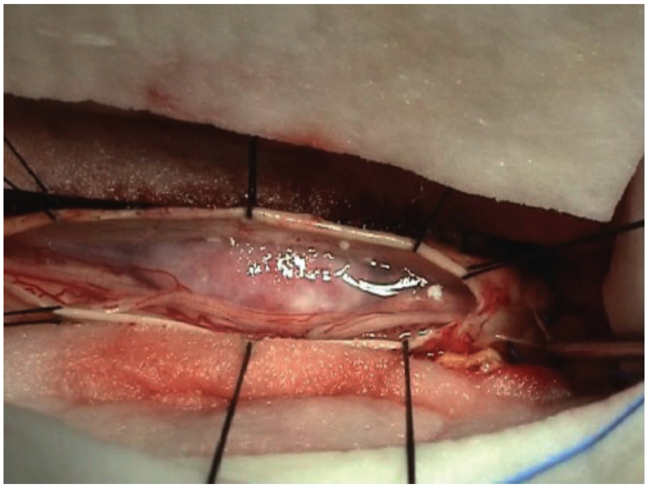


Plate 15.3 Operative photograph of intradural microscopic exploration of spinal meningioma with overlying arachnoid intact. Stay sutures hold dura opening, tumour arises from anterolateral dura mater.

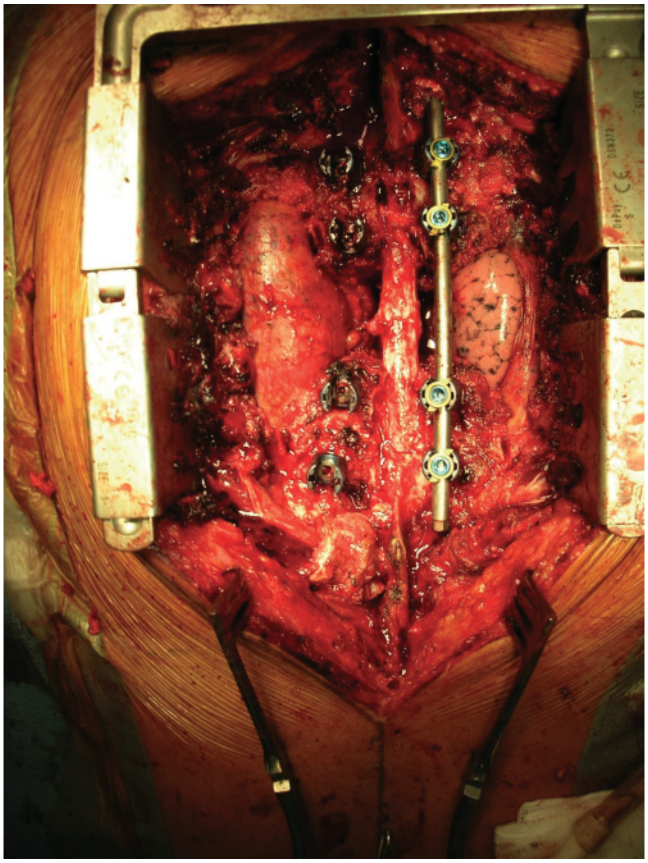


Plate 15.4 Operative photograph showing TOMITA™ spinal fixation.

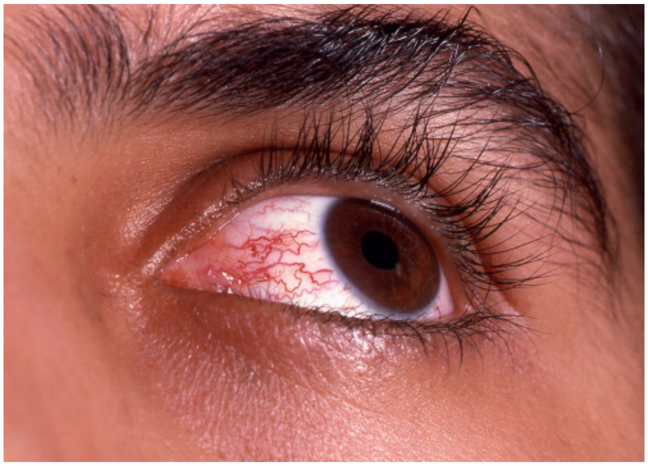


Plate 16.1 Conjuctival telangiectasia in a case of ataxia telengiectasia. (Courtesy of The Audio Visual Services Unit, National Hospital for Neurology & Neursurgery.)

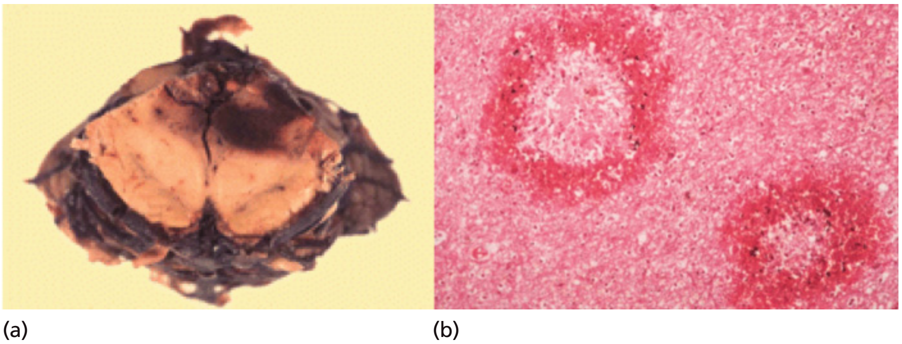


Plate 18.1 Fatal high-altitude cerebral oedema. (a) Brainstem showing haemorrhagic infarction; (b) ring haemorrhages in cerebral white matter. (From Clarke 2006, with permission.)

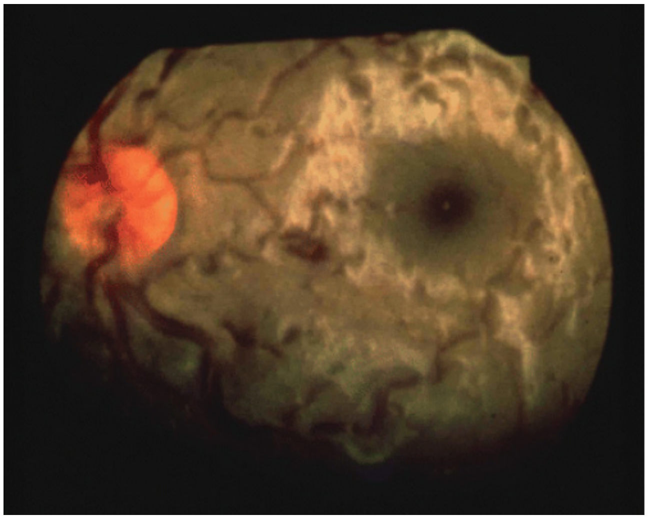


Plate 18.2 Abrupt cerebral oedema at extreme altitude – papilloedema, retinal oedema and venous congestion; Mount Everest SW Face, 1975. (From Clarke 2006, with permission).

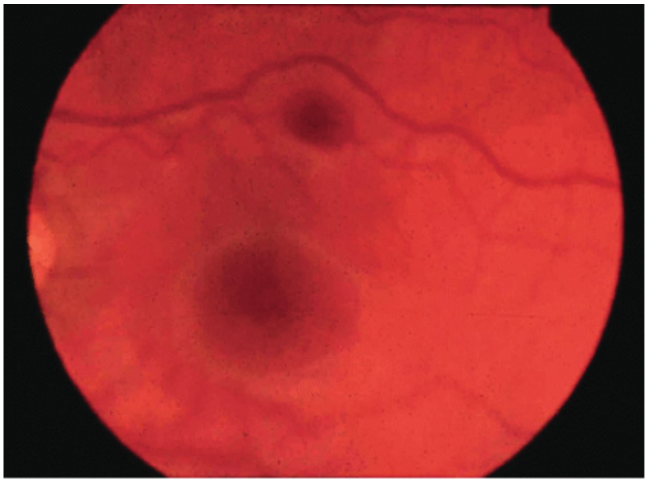


Plate 18.3 Symptomless retinal haemorrhages at 5500 m; Mount Everest, 1975. (From Clarke 2006, with permission.)

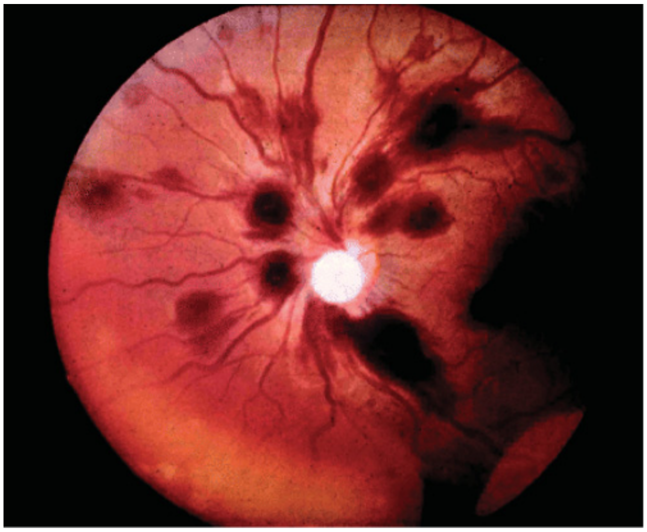


Plate 18.4 High altitude retinopathy with permanent visual loss. Retina showing extensive haemorrhagic change. (From Clarke 2006, with permission.)

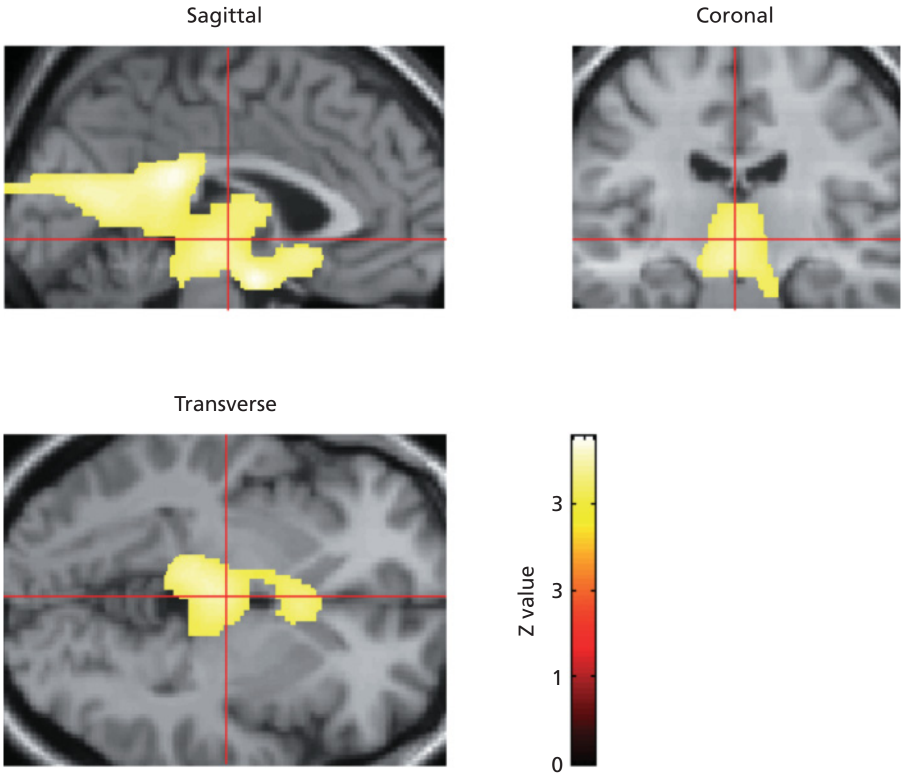


Plate 18.5 FDG-PET scan showing hypometabolism in Korsakoff patients with significant reduction of signal in thalamus, ventromedial cortex and retrosplenium. (From Reed *et al.* 2003. Courtesy of Professor M. Kopelman, St. Thomas' Hospital.)

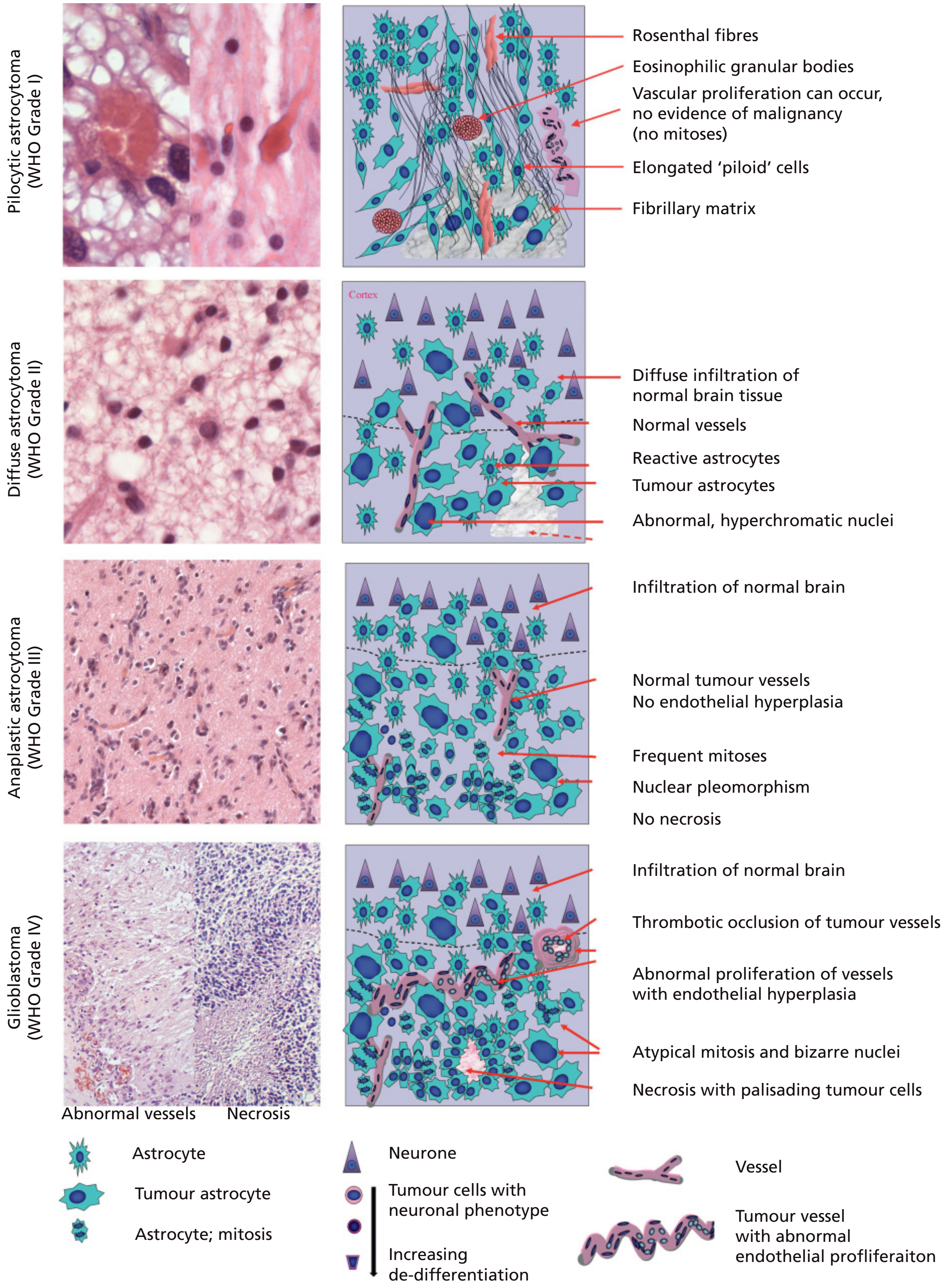

Pilocytic astrocytoma (WHO Grade I)
Rosenthal fibres
Eosinophilic granular bodies
Vascular proliferation can occur, no evidence of malignancy (no mitoses)
Elongated 'piloid' cells
Fibrillary matrix
Diffuse astrocytoma (WHO Grade II)
Cortex
Diffuse infiltration of normal brain tissue
Normal vessels
Reactive astrocytes
Tumour astrocytes
Abnormal, hyperchromatic nuclei
Anaplastic astrocytoma (WHO Grade III)
Infiltration of normal brain
Normal tumour vessels
No endothelial hyperplasia
Frequent mitoses
Nuclear pleomorphism
No necrosis
Glioblastoma (WHO Grade IV)
Infiltration of normal brain
Thrombotic occlusion of tumour vessels
Abnormal proliferation of vessels with endothelial hyperplasia
Atypical mitosis and bizarre nuclei
Necrosis with palisading tumour cells
Abnormal vessels
Necrosis
Astrocyte
Tumour astrocyte
Astrocyte; mitosis
Neurone
Tumour cells with neuronal phenotype
Increasing de-differentiation
Vessel
Tumour vessel with abnormal endothelial profliferaiton

Plate 20.1 Histological features of WHO Grade I–IV astrocytomas.

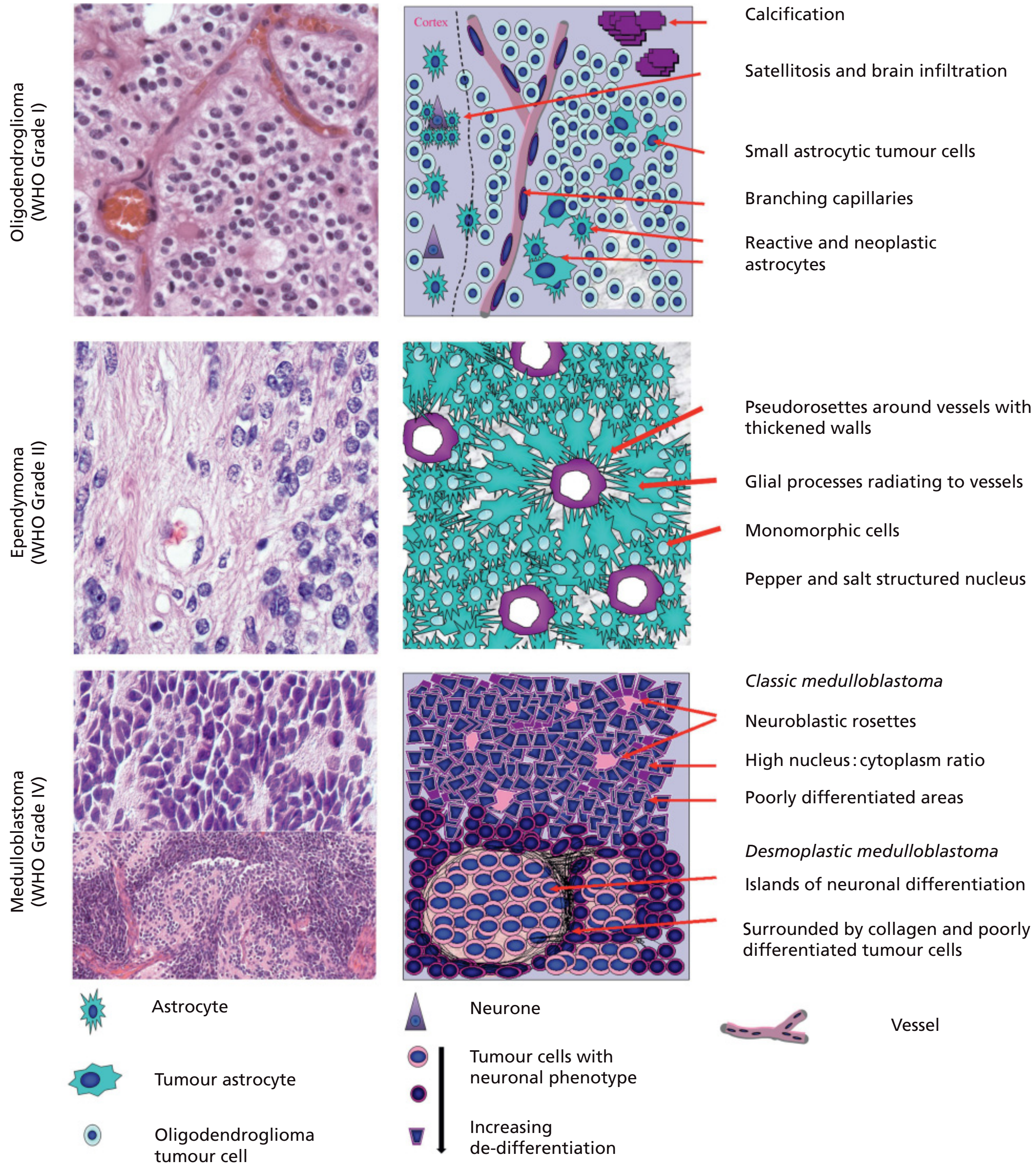
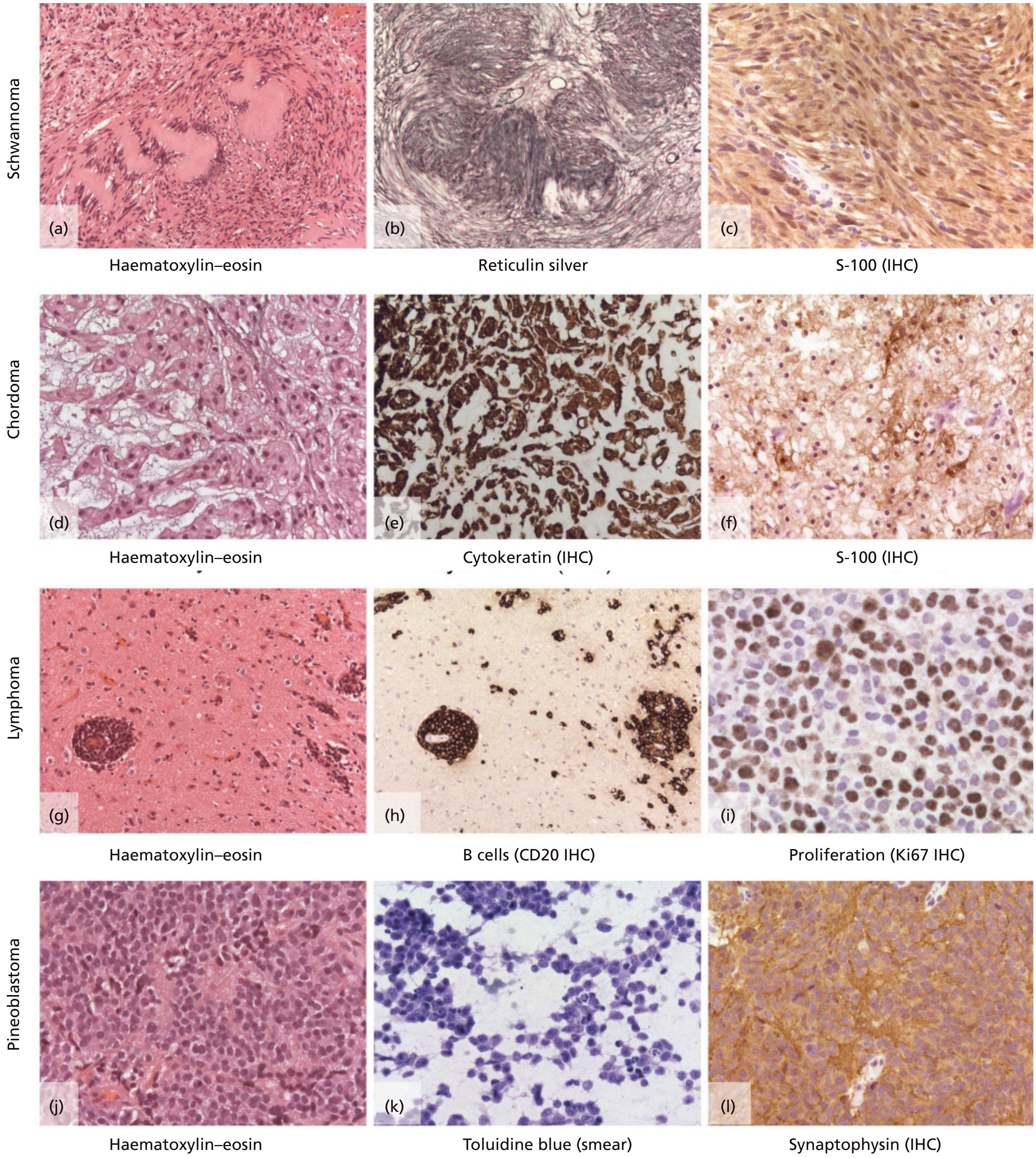

Oligodendroglioma (WHO Grade I)
Ependymoma (WHO Grade II)
Medulloblastoma (WHO Grade IV)
Cortex
Calcification
Satellitosis and brain infiltration
Small astrocytic tumour cells
Branching capillaries
Reactive and neoplastic astrocytes
Pseudorosettes around vessels with thickened walls
Glial processes radiating to vessels
Monomorphic cells
Pepper and salt structured nucleus
Classic medulloblastoma
Neuroblastic rosettes
High nucleus : cytoplasm ratio
Poorly differentiated areas
Desmoplastic medulloblastoma
Islands of neuronal differentiation
Surrounded by collagen and poorly differentiated tumour cells
Astrocyte
Tumour astrocyte
Oligodendroglioma tumour cell
Neurone
Tumour cells with neuronal phenotype
Increasing de-differentiation
Vessel

Plate 20.2 Histological features of three common intrinsic brain tumours.


Schwannoma
(a)
(b)
(c)
Chordoma
(d)
(e)
(f)
Lymphoma
(g)
(h)
(i)
Pineoblastoma
(j)
(k)
(l)

Haematoxylin–eosin Reticulin silver S-100 (IHC)

Haematoxylin–eosin Cytokeratin (IHC) S-100 (IHC)

Haematoxylin–eosin B cells (CD20 IHC) Proliferation (Ki67 IHC)

Haematoxylin–eosin Toluidine blue (smear) Synaptophysin (IHC)

Plate 20.3 Histological features of schwannoma, chordoma, lymphoma and pineoblastoma.

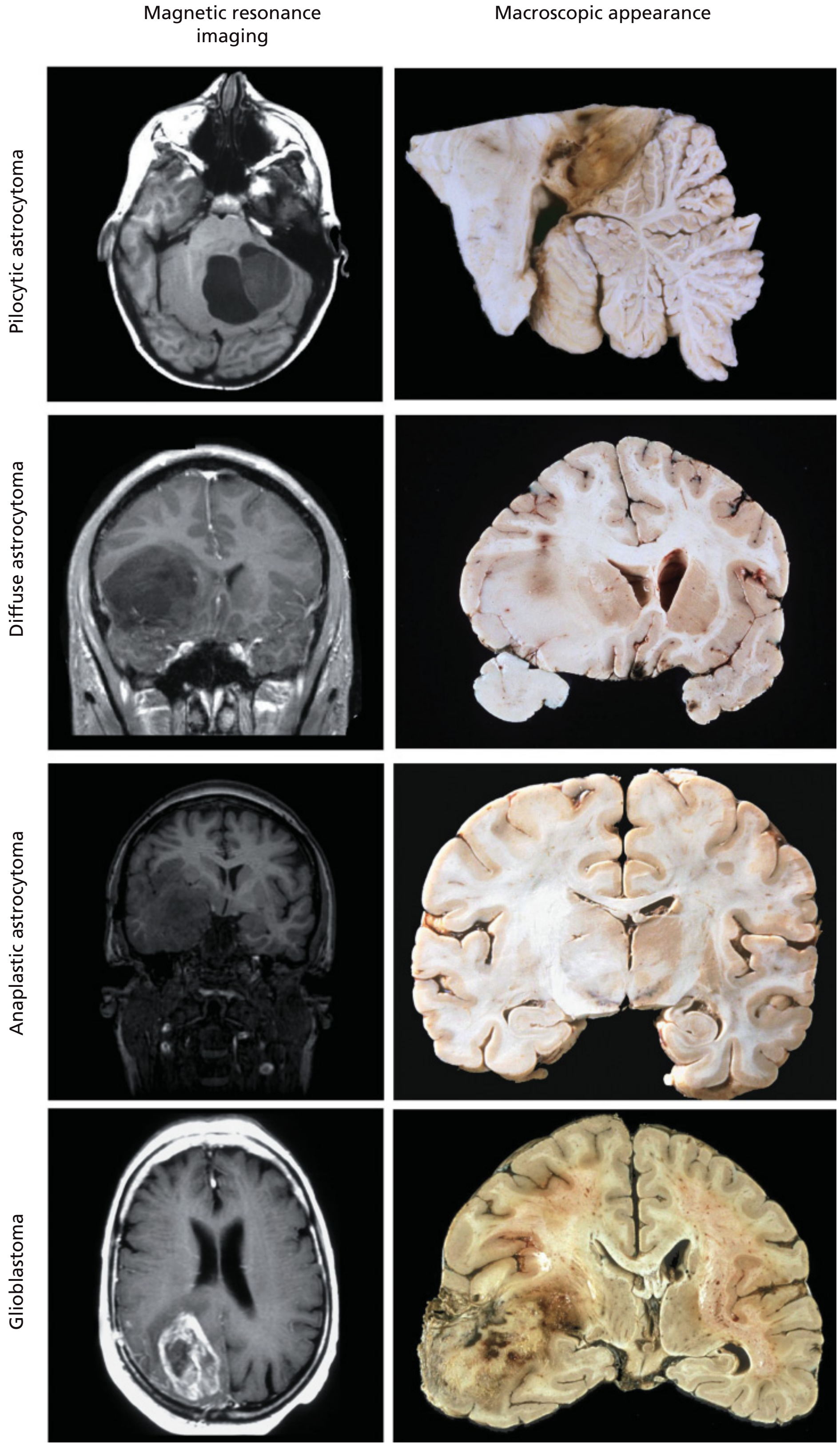

Magnetic resonance imaging
Macroscopic appearance
Pilocytic astrocytoma
Diffuse astrocytoma
Anaplastic astrocytoma
Glioblastoma

Plate 20.4 Imaging and macroscopic appearance of gliomas.

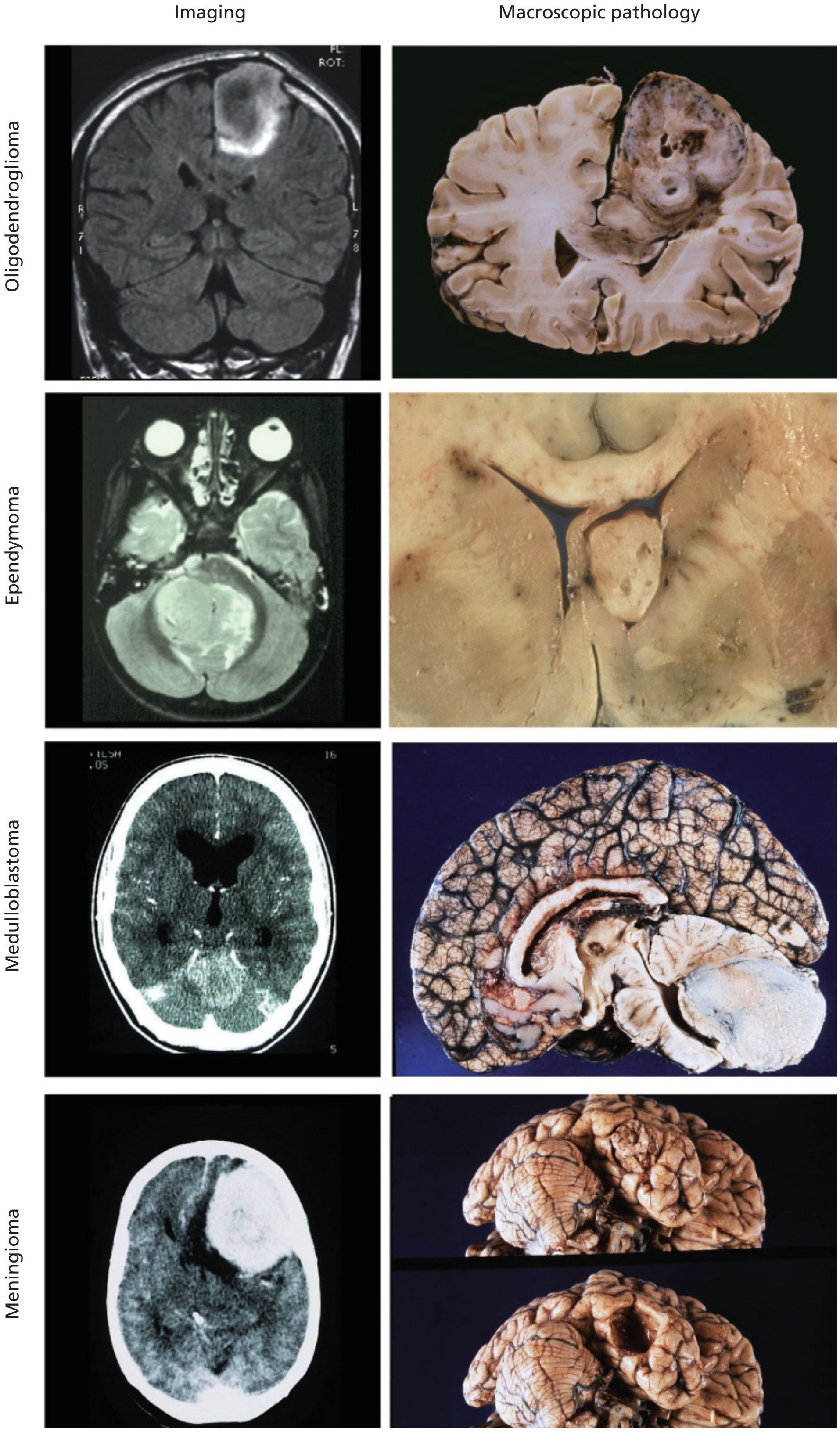
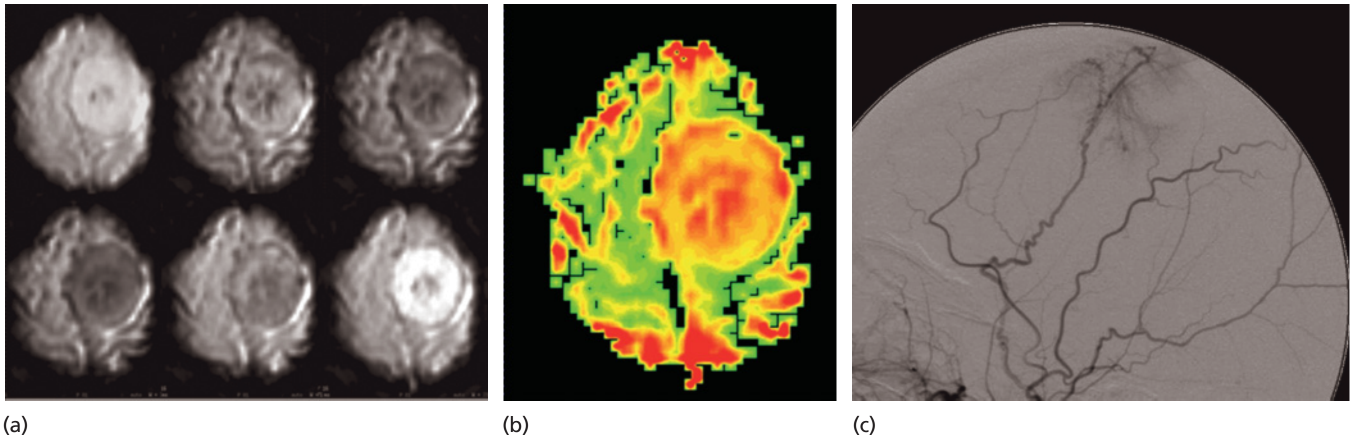
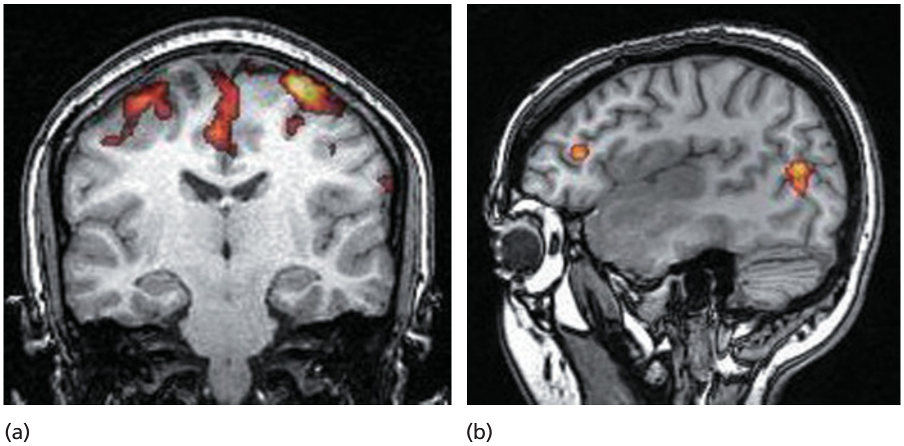

Imaging
Macroscopic pathology
Oligodendroglioma
Ependymoma
Medulloblastoma
Meningioma

Plate 20.5 Imaging and macroscopic appearance of common brain tumours.



(a) (b) (c)

Plate 20.6 (a) Selection of magnetic resonance (MR) perfusion source images from a frontal parasagittal meningioma, showing marked decrease of signal intensity within the tumour during the first pass of contrast medium bolus, indicating increased tumour vascularity. (b) Corresponding colour map of relative cerebral blood volume (rCBV). Red areas indicate regions of most markedly elevated rCBV within the tumour and over brain surface vessels. (c) External carotid artery angiogram shows tumour blush and confirms increased vascularity of the meningioma.



(a) (b)

Plate 20.7 (a) Coronal functional magnetic resonance imaging (fMRI) during opening and closing of hand in a patient with right superior frontal gyrus low-grade tumour. (b) Sagittal fMRI during picture naming task in a patient with a peri-insular tumour showing activity in Broca's area and in the visual cortex remote from the tumour.

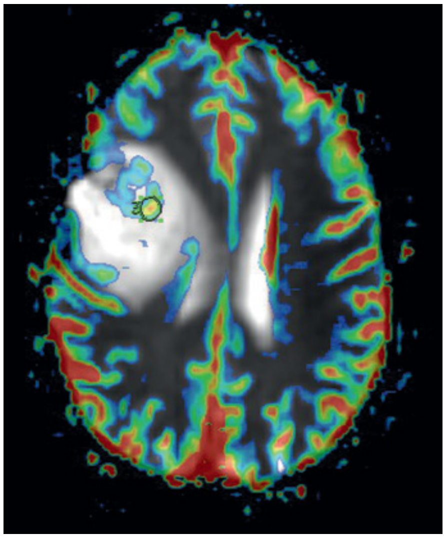
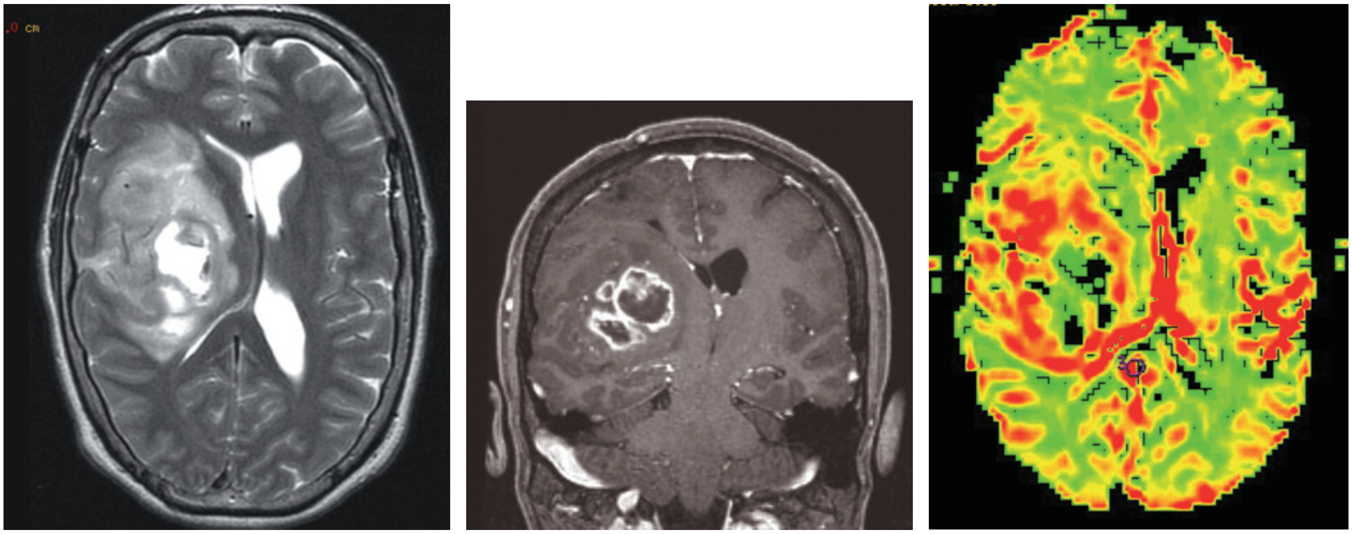
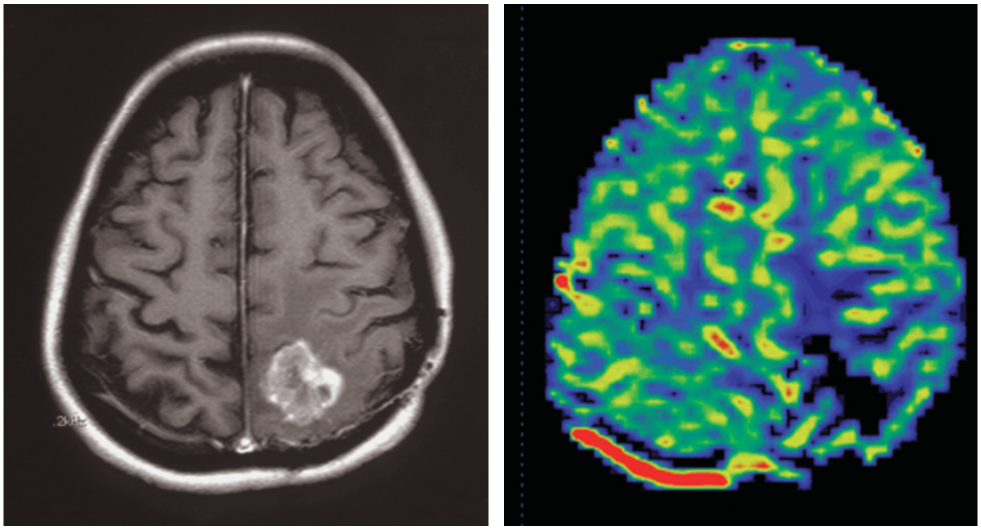


Plate 20.8 Relative cerebral blood flow (rCBV) colour overlay map in a low-grade oligodendroglioma showing area of increased rCBV in the anterior part of the tumour.



(a) (b) (c)

Plate 20.9 (a) T2 images of a high-grade oligodendroglioma showing a heterogeneous mass with a necrotic centre. (b) The contrast-enhanced T1 image demonstrates irregular ring enhancement within the mass. (c) On rCBV map large intra-tumoural areas of increased blood volume (in red) indicate areas of neovascularity.



(a) (b)

Plate 20.10 (a) Radiation necrosis following radiotherapy for a high-grade glioma. Contrast-enhanced T1 images show a brightly enhancing left parietal mass, indistinguishable from recurrent glioma. (b) rCBV shows mass has a decreased blood volume compared to normal white matter and appears dark, in keeping with radiation necrosis. A recurrent glioma is likely to have shown an elevated rCBV.

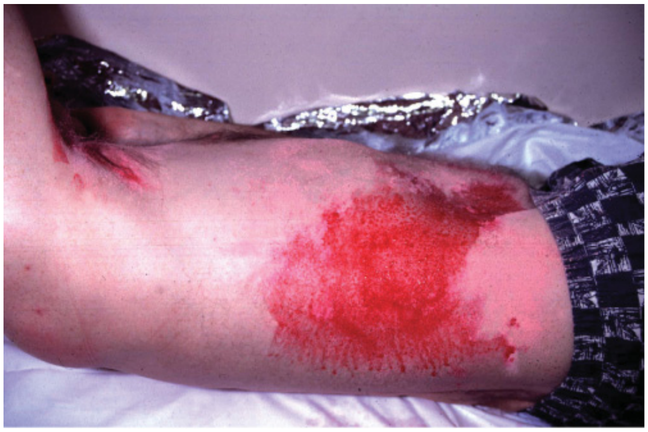
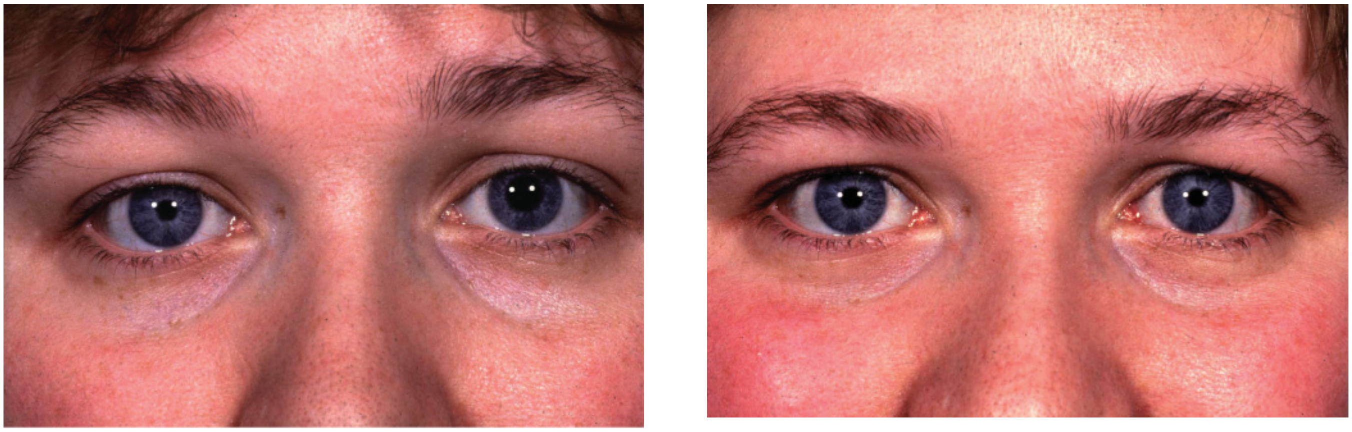


Plate 23.1 Segmental hyperhidrosis as a presenting feature in a patient in whom there were large areas without sweating. He had the Holmes–Adie syndrome with Ross's variant. (From Mathias 1998, with permission.)



Plates 23.2 (*left*) and **Plate 23.3** (*right*) Pupillary dilatation in Holmes–Adie syndrome and its response to pilocarpine. In Plate 23.2, the left pupil is clearly the larger – there is a diminished response to light. In Plate 23.3, the pupillary response to dilute pilocarpine (constriction) is greater on the left than in the normal right eye. (From Mathias 1998, with permission.)

1

Neurology Worldwide: the Burden of Neurological Disease

Simon Shorvon

Neurological disease casts a heavy shadow on the lives of the patient, their family and friends and on society. The aim of all neurological services should be to alleviate the suffering associated with the disease, and to realize this aim the rational planning of such health services requires knowledge in four broad areas. First, information is required about the epidemiology of the condition – its frequency and distribution within a population, its causation, mortality and co-morbidity. Second, it is important to know the broad impact of the disease (the 'burden of illness') on individuals, families and on health services and societies and also its financial cost. Third, data are needed on the effectiveness (and cost-effectiveness) of diagnostic, investigatory and treatment interventions. Finally, knowledge is required of the existing health care resources and their distribution and priorities. The last two areas are outside the scope of this chapter, and here a necessarily extremely brief overview of selected issues related to the epidemiology and burden of illness is given, where possible using figures derived from studies from the National Hospital in London. These set the scene for the more detailed consideration of neurological disease contained in the rest of the volume.

Epidemiology of neurological disease

It is self-evident that knowledge of epidemiology will be important to underpin any decision about the provision of health care resources. It is also clear that epidemiological data (on frequency, distribution, mortality, etc.) are of little value unless related to an intervention or therapeutic advance. Epidemiclogical data is particularly valuable for resource provision. Sadly, however, in practice, even where reliable data exist, these are used only inconsistently in planning health care. It is for this reason that in many, indeed perhaps most, health care settings, the provision of facilities for neurological care is often surprisingly fragmented and inappropriately targeted.

Frequency and distribution of neurological disease

Incidence and prevalence are the most common measures of frequency used in medicine.

Incidence is defined as the rate at which new cases occur in a specified population during a specified period. The incidence rate is usually calculated as the number of new cases occurring per 100,000 of the general population per year.

Prevalence is defined as proportion of a population that are cases at a point in time. The prevalence rate is usually calculated as the number of existing cases per 1000 of the general population. Point prevalence is calculated as the number on a particular day (prevalence day) and period prevalence is calculated as the number in a population over a specified period of time. Lifetime prevalence is defined as the risk of acquiring the condition at any time during life and is another important figure.

For many neurological diseases, information on even these basic measures is incomplete. Furthermore, the frequency of many neurological disorders varies markedly in different geographical regions, differs in urban when compared with rural settings, may differ with ethnicity, and is of often linked to lifestyle and socio-economic factors.

In most neurological illnesses there are also striking differences in frequency at different ages, and so the age distribution of the population will affect the frequency, and some diseases have marked gender differences. For these reasons, age-specific or sex-specific rates, or frequency estimates in restricted age ranges, are generally more informative than crude rates. For instance, the annual incidence of stroke in a population is about 190/100,000/year, but in the population over 65 years the rate is 1100/100,000/year. Similarly, the incidence and prevalence of Parkinson's disease in the general population is 20/100,000/year and 2/1000, and in those over 65 years is 160/100,000/year and 10/1000.

Changes in age structure in populations will impact heavily on the number of patients with diseases that have age-specificity. In most developing countries, the population has a far greater proportion of children and young adults than in developed countries (Figure 1.1 shows age structures in a typical developed [Sweden]

Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

and developing country [Costa Rica]). It is also important to recognize that although worldwide human populations are growing in an exponential fashion, growth rates vary widely among different countries and regions and the concept of 'doubling time' is a useful way of quantifying this. Doubling time – the time it is predicted to take for a population to double in size – depends not only on population size and mortality rates, but also on the number of children per woman (Table 1.1) and various other social and health parameters.

The approximate non-standardized figures for the prevalence and incidence of neurological disorders in a developed country are shown in Table 1.2. This table illustrates one other important point – that for chronic diseases, as for many neurological diseases, the incidence rates may be low but prevalence rates are high. This is important for health service planning, as the facilities required for incident cases are very different from prevalent cases. The former require provision for investigation and acute therapy and the latter largely for follow-up, social care, long-term therapy and rehabilitation.

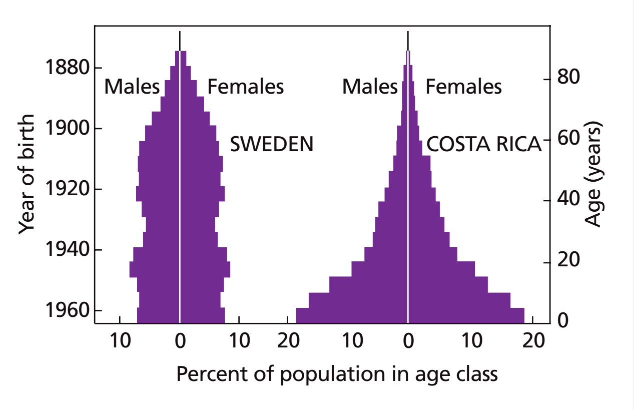


Figure 1.1 Age structure in developed (Sweden) and developing (Costa Rica) countries. (From Worldwatch Database (1996), with permission.)

The results of age-adjusted incidence and prevalence figures in a population of 100,230 persons in a selection of general practices served by the National Hospital for Neurology and Neurosurgery in London from a research project published in 2000 are shown in Tables 1.3–1.5. Here, the rates are adjusted for age to reflect the general UK population and are given alongside comparative results from other studies. Overall, the onset of 625 neurological disorders was observed per 100,000 population during the year of observation. Six per cent of the population in whom lifetime prevalence was surveyed had had a neurological disorder. In the UK, diseases of the nervous system accounted for 7.6% of all GP consultations between 1981 and 1982. The frequency of disability in private households amongst those over 16 years of age in the UK in 1971 was comprehensively delineated in the Harris Report. Disabilities relevant to neurology – CNS disorders, muscular dystrophies, congenital malformations of the spine and hydrocephalus, cerebral birth injury, senility as a cause of cognitive disability – occurred with a prevalence of 78/1000. The UK Office for Population Censuses and Surveys (OPCS) survey of disability 16 years later graded disability according to severity as well as overall frequency. The prevalence of complaints relevant to neurology was 13% for 'CNS disorders', 2% each for dementia and mental retardation, and 6% for back complaints. In a later study, 'CNS complaints' accounted for 7% of disability overall but for 16% of conditions with a high severity score. Roughly similar figures are found elsewhere. Population-based estimates from the USA, for instance, report point prevalence rates of neurological conditions (excluding headache, back pain and discs, mental retardation, psychosis, non-neurological visual and hearing loss and nervous system trauma) of 3.6/100.

It is therefore clear that neurological diseases are common and cause significant degrees of disability. Furthermore, the existing figures are probably underestimates, as there are many difficulties associated with the collection of statistics in neurology, leading mainly to under-ascertainment. Such issues apply to epidemiological studies in all areas, but in addition to the varied general issues there is one particular problem for neurology that requires

Table 1.1 Population size in selected developing and developed countries – doubling time.

Country	Approximate population size (millions)	Fertility (mean number of children per woman)	Doubling time* (years)
Germany	81	1.40	–654
Japan	125	1.50	217
USA	258	2.00	92
China	1178	1.90	60
Mexico	90	3.40	30
Philippines	65	4.10	28
Iran	63	6.60	20
Nigeria	95	6.60	23

* Doubling time is the predicted time it will take for the population to double in size. The doubling time depends on population size, age structure, number of children per women and mortality rates. These figures were taken from the WorldWatch database, and predate improvements in child health, reductions in mortality rates amongst children and young adults and the HIV epidemic. A negative number implies a shrinking population.

Table 1.2 Annual incidence and point prevalence figures of common neurological disorders (1984). Data derived from Kurtzke 1982; Hopkins 1993; Hughes 2002; Zakrzewska & Hamlyn 1999; Hirtz *et al.* 2007 and other sources. The table includes only those conditions with an incidence above 1/100,000/year; whole populations considered, without age standardization, and excludes shingles.

Disorder	Incidence (per 100,000 persons/year)	Point prevalence (per 100,000 persons)
Migraine	370	12,100
Acute stroke	190	900
Epilepsy	50	710
Febrile convulsions	50	
Dementia	50	250
Chronic polyneuropathy (all types)	40	24
Transient ischaemic attacks	30	
Bell's palsy	25	
Parkinson's disease	20	200
Meningitis	15	
Subarachnoid haemorrhage	15	
Metastatic brain tumour	15	
Primary brain tumour	5	6
Trigeminal neuralgia	4	1
Multiple sclerosis	4	90
Motor neurone disease	2	4
Acute post infectious polyneuropathy	2	1
All muscular dystrophies	1	6

Table 1.3 The National Hospital for Neurology and Neurosurgery (NHNN) record linkage study: age- and sex-adjusted incidence rates for neurological conditions, compared with previously reported rates.

Conditions	NHNN linkage age- and sex-adjusted rate (95% CI)/100,000/year	Previously reported incidence rates/100,000/year
Stroke		
First cerebrovascular episode	205 (183–230)	200
Second cerebrovascular episode	42 (33–55)	28–35
Intracranial haemorrhage	10 (5–17)	5% of stroke, i.e. 10
Seizure disorders		
Epilepsy	46 (36–60)	24–53
Single seizures	11 (7–18)	20
Tumours		
Primary CNS tumours (benign and malignant)	10 (5–18)	7; 15
Parkinson's disease	19 (12–27)	12–18
Compressive mononeuropathies – all except carpal tunnel syndrome (CTS)	49 (39–61)	40
Arm – all excluding CTS	24 (17–33)	
Leg – all	20 (14–29)	
Polyneuropathies		
Diabetic polyneuropathy	54 (33–83)	40
All excluding diabetic and alcoholic	15 (9–23)	11
Shingles	140 (104–184)	71; 131; 400; 480
Post herpetic neuralgia	11 (6, 17)	13; 34; 9% of shingles
Bacterial CNS infection (overall)	7 (4–13)	10; 11
Essential tremor	8 (4–14)	24

Continued on p. 4

Table 1.3 *Continued*

Conditions	NHNN linkage age- and sex-adjusted rate (95% CI)/100,000/year	Previously reported incidence rates/100,000/year
Trigeminal neuralgia	8 (4–13)	2; 4
Benign CNS tumour	7 (3–13)	10
Multiple sclerosis	7 (4–11)	2–8
Severe head injury	7 (3–12)	4–6
Subarachnoid haemorrhage	7 (3–12)	10–15
Subdural haematoma	6 (3–12)	
Cluster headache	6 (3–10)	10 (6–14)
Cranial nerve disorder (excluding II, III, IV, VI, Bell's palsy or trigeminal neuralgia)	6 (2, 12)	
Disorders of II, III, IV, VI, including pupillary abnormalities but not optic neuritis	6 (3–11)	
Aseptic meningitis	5 (2–9)	1; 11 (10–12)
Metastatic CNS tumour	4 (1–9)	14 (12, 16); 15
Presenile dementia	4 (2–9)	
Cerebral palsy	3 (1–8)	1.5; 2.7; 9
Neonatal encephalopathy or stroke	3 (1–8)	
Other congenital CNS abnormalities	3 (1–8)	7
Brachial neuritis	3 (1–7)	2
Guillain–Barré syndrome	3 (1–6)	1–2
Myasthenia gravis	3 (0.8–7)	0.25–0.8; 1
Primary malignant CNS tumour	3 (0.7–7)	5 (F) 6 (M); 5
Transient global amnesia	3 (0.5–7)	
Spinal cord injury	3 (0.9–7)	1.3–4; 5
Acute cervical myelopathy related to disc	2 (0.2–6)	
Cranial nerve injury	2 (0.5–5)	
Demyelination disorders not limited to optic nerve and not fulfilling criteria for MS	2 (0.4–5)	1.2
HIV encephalopathy	2 (0.8–5)	
Idiopathic myelopathy	2 (0.4–6)	
Motor neurone disease	2 (0.3–5)	1–2
Spondylitic myelopathy (chronic)	2 (0.5–6)	
Truncal mononeuropathy	2 (0.6–6)	
Diabetic amyotrophy	1 (0.1–4)	
Focal dystonia	1 (0.1–4)	2.2
Non-cervical disc-related cord or cauda equine damage (i.e. other disc or anatomical anomalies)	1 (0.1–3)	1.6; 3
Optic neuritis	1 (0.2–3)	
Spinal malformation	1 (0.1–2)	3.3

A small number of cases of the following diseases were also found in this study: cerebellar degeneration, dementia of uncertain cause, frontal dementia with anterior horn cell disease, neurosarcoid with cord involvement, neurofibromatosis, tuberous sclerosis, communicating hydrocephalus, aqueduct stenosis, cerebral cyst, tonsillar herniation with Chiari malformation, syringomyelia, myotonic dystrophy, myositis, idiopathic neurogenic bladder, tubercular meningitis, meningococcal meningitis, syphilis, streptococcal meningitis, *Streptococcus pneumoniae* brain abscess, *Listeria* meningitis, cryptococcal meningitis, and an unidentified ventriculitis in a man dying of a reticulosis).

Table 1.4 The National Hospital for Neurology and Neurosurgery record linkage study: lifetime prevalence of neurological conditions, and previously reported rates.

Conditions	Lifetime prevalence/1000 population (95% CI)	Previously reported point prevalence (PP) rates or estimated lifetime prevalence/1000
Stroke	9 (8–11)	5
Transient ischaemia	5 (4–6)	2; 6
Epilepsy	4 (4–5)	5
Congenital neurological deficit	3 (3–4)	3, 2/1000 between 7 and 10 years; CNS malformation 0.7, Down's syndrome 0.5
Parkinson's disease	2 (1–3)	1 (PP); 2 (1); 2
Multiple sclerosis	2 (2–3)	1; 2
Diabetic polyneuropathy	2 (1–3)	3
Compressive mononeuropathies (except CTS)	2 (2–3)	0.4 (PP)
Subarachnoid haemorrhage	1 (0.8–2)	0.5
Polyneuropathy (excluding diabetic and alcoholic)	1 (0.8–2)	0.4 (PP)
Single seizures	1 (0.9–2)	
Bacterial meningitis	1 (0.8–2)	abscess 0.02 (PP), meningitis 0.05 (PP)
Other meningitis or encephalitis	1 (1–1)	
Aseptic meningitis	0.9 (0.6–1)	
Essential tremor	0.8 (0.5–1)	3 (1)
Polio	0.7 (0.4–1)	
Severe head injury	0.6 (0.4–1)	1
Optic neuritis	0.6 (0.3–1)	0.1
Benign CNS tumours	0.5 (0.3–1)	0.6 in brain, 0.1 in cord
Intracranial haemorrhage	0.5 (0.2–0.8)	
Other movement disorders	0.4 (0.2–0.7)	Hereditary ataxia 0.08
Viral encephalitis	0.4 (0.2–0.7)	0.1
Spondylitic and compressive myelopathy	0.4 (0.2–0.7)	
Cluster headache	0.3 (0.2–0.6)	0.3 (F), 1 (M, M + F)
Subdural haemorrhage	0.3 (0.2–0.6)	
Malignant CNS tumours	0.2 (0.06–0.4)	Primary malignant 0.05; metastatic in brain 0.15, 0.05 in cord
PN or plexus injury	0.2 (0.05–0.4)	0.3
Demyelinating conditions not fulfilling the criteria for MS	0.1 (0.04–0.3)	
Cauda equina lesion	0.1 (0.02–0.4)	
Dystonia primary/secondary	0.1 (0.02–0.4)	0.3
	0.1 (0.03–0.3)	
Benign intracranial hypertension	0.1 (0.02–0.3)	
Intrinsic myelopathy	0.1 (0.02–0.3)	Syrinx 0.07, 0.06
Spinal cord injury	0.1 (0.02–0.3)	0.5, 0.8
Narcolepsy	0.1 (0.02–0.3)	
Motor neurone disease	0.1 (0.01–0.3)	0.04–0.1; 0.06
Aqueduct stenosis and hydrocephalus in adults	0.1 (0.01–0.3)	
HTLV 1 myelopathy	0.04 (0–0.2)	
Transient global amnesia	0.04 (0–0.2)	
Leg mononeuropathy – all	1 (0.8–2)	
Arm mononeuropathy – all excluding CTS	0.7 (0.5–1)	
Trigeminal neuralgia	0.7 (0.4–1)	0.4
Post-herpetic neuralgia	0.7 (0.4–1)	
Muscular dystrophies	0.4 (0.2–0.7)	0.02–0.05; 0.6
Myasthenia gravis	0.4 (0.2–0.7)	0.04–0.1; 0.08, 0.1 (0.08–0.2); 0.4
Eye movement disorders	0.3 (0.2–0.7)	
Brachial neuritis	0.3 (0.1–0.6)	
Guillain–Barré syndrome	0.2 (0.08–0.5)	0.08
Horner's syndrome	0.2 (0.04–0.4)	

Continued on p. 6

Table 1.4 *Continued*

Conditions	Lifetime prevalence/1000 population (95% CI)	Previously reported point prevalence (PP) rates or estimated lifetime prevalence/1000
Other mononeuropathy	0.1 (0.04–0.3)	
Pupillary abnormalities	0.08 (0.01–0.3)	
Sacral plexitis/plexopathy	0.04 (0–0.2)	

CTS, carpal tunnel syndrome; HTLV 1, human T-lymphotrophic virus type 1; MS, multiple sclerosis; PN, peripheral nerve.
Shingles was excluded from this survey of lifetime prevalence.

Table 1.5 The National Hospital for Neurology and Neurosurgery record linkage study: age-specific incidence rates for stroke, epilepsy and Parkinson's disease.

Age band	Incidence rates /100,000/year by age band adjusted to the UK population				
	First stroke		Epilepsy M + F	Single seizures M + F	Parkinson M + F
	Men	Women			
0–4			86	32	
5–9			46	12	
10–14			94		
15–19			52		
20–24			33	16	
25–29			19	19	
30–34			24	5	
35–39			54	14	
40–44	35	82	18	9	
45–49	194		50	10	20
50–54	240	167	50		
55–59	560	203	31	15	
60–64	1051	629	34	34	50
65–69	817	940	37		37
70–74	850	926	142		222
75–79	972	1271	50	25	100
80–84	806	890	32		
85–89	299	757	29	29	116
>90					
>40	467	446			

mention. This is the difficulty of 'case definition' (and thus case ascertainment). Many neurological disorders are defined on clinical criteria, with the inevitable subjectivity this entails. Thus, boundaries exist in which symptoms are occurring without formal diagnosis – for instance, the boundaries between ageing and Alzheimer's disease and between chronic headache and migraine. Similarly, in epilepsy, the inclusion of febrile seizures, single seizures and acute symptomatic seizures within a definition of epilepsy will more than double frequency figures. In some neurological disorders, only 'the tip of the iceberg' cases are known to health care professionals, a common effect in conditions that are only mildly symptomatic in their early stages, such as migraine, some neuropathies, some dementing illnesses and Parkinson's disease. Severity also varies markedly, and the inclusion of mild cases will greatly inflate frequency figures but with relative reduction in burden of illness. Studies of epilepsy from the National Hospital provide examples of this – with over 60% of patients with epilepsy entering long-term remission and incurring only a minor impact on health services (see below). Case finding methods also need to be tailored to the disease's spectrum of severity and frequency, and any method using hospital statistics will greatly underestimate the true number of cases as many minor or static neurological conditions are cared for outside the hospital setting.

Ethnic differences in disease were shown by the study of Stewart *et al.* from a multi-ethnic region of London in stroke. A stroke register was used with 12 sources of case ascertainment. The population size was 234,533 with 72% Caucasian, 21% Black (11% Afro-Caribbean, 7.5% West African and 2.5% mixed) and 3% South Asian. Incidence rates were standardized for age and sex. The crude annual incidence rate of stroke was 130 (120–141/100,000/year and the age-adjusted rate figure (to a standard European population) is 125 (115–135). The rate in the Black population was significantly higher with an incidence rate of 221 (177–276 per 100,000). The rate, not surprisingly, increased with age. The study also looked at social class and found higher rates in those less than 64 years in lower social classes. This sort of study generates hypotheses about causation (as yet not explained) and provides data for rational health care planning (partially implemented).

Similar considerations apply when considering rarer conditions, especially those requiring complex medical care where a sound estimate of frequency is important. A study of the prevalence and causation of dementia in those under 65 years, carried out by Harvey *et al.* in West London, is one example. In this population of 567,500 people, the prevalence of dementia in those aged 30–64 years was 0.54/1000 (0.45–0.64). For those aged 45–64 years, the prevalence was 0.98/1000 (0.81–1.18). From the age of 35 onwards, the prevalence of dementia was found to approximately double with each 5 year increase in age. On the basis of these figures, it was estimated that in 2003, there were 18,319 (15,296–21,758) people with dementia under the age of 65 in the UK. Using diagnostic algorithms, 34% had Alzheimer's disease, 18% vascular dementia, 12% fronto-temporal dementia, 7% dementia with Lewy bodies and 19% had other causes which included Huntington's disease, multiple sclerosis, corticobasal dementia, prion disease, Down's syndrome (probably underestimated), Parkinson's disease and others.

From the perspective of health services, figures of prevalence and incidence of the cases receiving treatment are important, as it is these cases that consume resources, not untreated (usually mild) or cases before diagnosis. In 1998, a large study of epilepsy was published by the author and colleagues amongst a population of 2,052,922 in England and Wales of persons with epilepsy receiving anti-epileptic drug treatment (Wallace, Shorvon & Tallis 1998). This provided accurate age-specific rates (Figure 1.2) and both the period prevalence and incidence of treated epilepsy was lower in children and higher in the elderly.

Neurology is also distinguished from other areas of medicine by the large number of uncommon conditions within its purview (neurology has the highest number of conditions listed in the International Classification of Diseases), and therefore large populations must be studied to obtain accurate population-based data with appropriate statistical reliability. Sampling error increases with rarer events and for many diseases there are few reliable data.

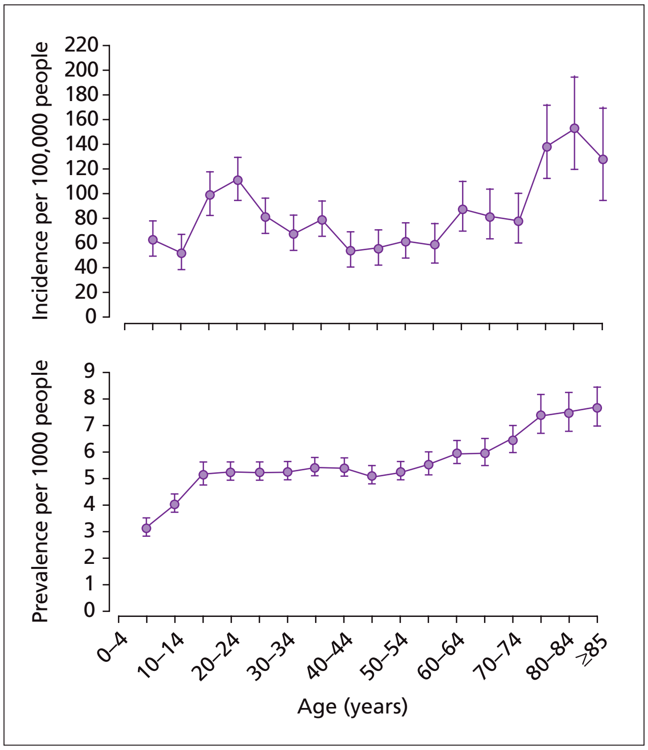


Figure 1.2 Standardized prevalence and incidence rates of treated epilepsy in a population of 2,052,922 persons in England and Wales in 1995. (Bars indicate 95% CI.) Prevalence of treated epilepsy: overall 5.15/1000 people (95% confidence interval [CI] 5.05–5.25); age 5–9 years 3.16 [2.86–3.48]; 10–14 years 4.05 [3.70–4.42], 65–69 years 6.01 [5.50–6.57]; 70–74 years 6.53 [5.97–7.14]; 75–79 years 7.39 [6.73–8.11]; 80–84 years 7.54 [6.78–8.39]; 85 years and older 7.73 [6.98–8.66]). Incidence of treated epilepsy: overall 80.8/100,000 people (76.9–84.7); 5–9 years 63.2 [50.5–79.1]; 10–14 years 53.8 [42.4–68.3]),` 65–69 years 85.9 [68.5–107.3]; 70–74 years 82.8 [65.0–105.2]; 75–79 years 114.5 [116.9–179.2]; 80–84 years 159 [125.2–202.6]; 85 years and older 135.4 [100.4–178.7]). (From Wallace, Shorvon & Tallis (1998), with permission.)

Causation

The attribution of causation to neurological disease is not always a simple matter. Most neurological diseases are multifactorial in nature, being the result of complex interactions between genetic and environmental influences. The balance between the two varies. The genetic influences can be very strong – for instance, in single gene disorders with high penetrance (e.g. Huntington's disease). In others the genetic influence is the result of more complex interactions between presumed susceptibility genes of which there may be many (e.g. epilepsy), and in other diseases identifiable Mendelian genetic influences do exist but are seen in some families cases only (Alzheimer's disease for instance is familial in about 10% of cases). The environmental influences are predominant in many diseases, for instance head injury or cerebrovascular disease. An interaction between genetic and environmental factors occurs in other diseases, for instance the interaction of smoking and genetic susceptibility in Parkinson's disease, or geographic location and genetic susceptibility in multiple sclerosis. The latter is an interesting example as there are often unexplained geographical variations which may reflect either environmental or genetic influences or both. In most neurological diseases, even the common diseases, the primary causes are not clearly understood (see Chapter 10).

In multifactorial disease, it is often helpful to define 'risk factors'. The study of the epidemiology of a disease, in particular using case–control methodologies, can give important clues as to relative importance of different risk factors. The use of risk factor, hazard ratio and odds ratio calculations allows meaningful comparative statistics to be drawn up. This is demonstrated by the example of epilepsy resulting from cerebrovascular disease. In one study, a history of stroke has been found to be associated with an increased lifetime occurrence of epilepsy (OR 3.3; 95% CI 1.3–8.5). Among the other vascular determinants, only a history of hypertension was associated with the occurrence of unprovoked seizures (OR 1.6; 95% CI 1.0–2.4). The risk of unprovoked seizures rises to 4.1 (95% CI 1.5–11.0) in subjects having a history of both stroke and hypertension. Haemorrhagic stroke (subarachnoid haemorrhage and, to a lesser extent, primary intracerebral haemorrhage) are followed by a higher risk of seizures. The cumulative probability of developing seizures after a first stroke is about 6% after 1 year and rises to 11% at 5 years, with significant differences across stroke subtypes (cerebral infarction 4 and 10%; primary cerebral haemorrhage 20 and 26%; subarachnoid haemorrhage 22 and 34%). The risk of epilepsy among survivors of subarachnoid haemorrhage caused by ruptured cerebral aneurysm is highest in patients with acute symptomatic seizures (RR 7.0; 95% CI 2.3–21.6) and those with severe neurological sequelae (RR 2.5; 95% CI 0.9–6.3). Another study by Wallace and colleagues compared the frequency of stroke after the development of late-onset seizures in 4709 individuals who had seizures beginning at or after the age of 60 years, with 4709 randomly selected, matched controls with no history of seizures. Log-rank testing, adjusted for matching, showed a highly significant difference in stroke-free survival between the two groups ($P < 0.0001$) and the relative hazard of stroke at any point for people with seizures compared with the control group was 2.89 (95% CI 2.45–3.41).

Mortality

The mortality rate of any condition is defined as the number of persons with that condition dying during a specified period divided by the number of persons in the same population. This information is of limited value, particularly in chronic neurological disease, without a knowledge of the underlying rate of death in patients without the condition or of age distribution. Therefore, mortality is often expressed as the ratio between the observed and expected numbers of death – this measure is known as the standardized mortality ratio (SMR). Expected deaths are calculated by measuring the death rates of a reference population with an age distribution that is similar to the study population. When there is no difference in mortality between the study and reference population the SMR is 1. The 95% CI provides an estimate of the significance of the calculated SMR. Another useful measure is the proportional mortality ratio which is the percentage of deaths that are due to any one cause. Life expectancy, defined as the median survival, is linked to age and is often lowered in neurological disease when compared with a healthy population, but statistics are complex to derive and there are few studies of this in neurological disease.

Taking epilepsy as an example, in a UK cohort study we followed a cohort of 564 newly diagnosed cases of epilepsy for 11–14 years and found an overall SMR of 2.1 (95% CI 1.8–2.4). Patients with acute symptomatic epilepsy (SMR 3.0; 95% CI 2.0–4.3), remote symptomatic epilepsy (SMR 3.7; 95% CI 2.9–4.6) and epilepsy due to congenital neurological deficits (SMR 25; 95% CI 5.1, 73.1) had significantly increased long-term mortality rates. In idiopathic epilepsy the SMR was 1.3 (0.9–1.9) – in other words not significantly different from the national population. The study also calculated the hazard ratio (HR), or risk of mortality in a particular group with a particular risk factor compared to another group without that particular risk factor. For epilepsy overall , it was 6.2 (95% CI 1.4–27.7; $P = 0.049$). Rates varied with the cause of epilepsy: cerebrovascular disease (HR 2.4; 95% CI 1.7–3.4; $P < 0.0001$), CNS tumour (HR 12.0; 95% CI 7.9–18.2; $P < 0.0001$), alcohol (HR 2.9; 95% CI 1.5–5.7; $P = 0.004$) and congenital neurological deficits (HR 10.9; 95% CI 3.2–36.1; $P = 0.003$). An older age at the time of diagnosis was also associated with significantly increased mortality rates (HR 1.9; 95% CI 1.7–2.0; $P < 0.0001$). Life expectancy has also been calculated in the same population based on the Weibull distribution. This depends on age at time of diagnosis and aetiological group, and of course reductions in life expectancy diminish over time. In our study of epilepsy, overall reduction in life expectancy, at the time of diagnosis, was found to be up to 2 years for people with a diagnosis of idiopathic or cryptogenic epilepsy, and up to 10 years in people with symptomatic epilepsy.

Mortality rates can be a useful way of quantifying treatment, but it is equally important in some neurological conditions to consider quality of life. This was well shown in a study of survival after radiotherapy in malignant glioma by Clarke and colleagues in 1996. Radiotherapy is known to prolong life (in one trial to 38 weeks after radiotherapy compared to 14 weeks with steroids alone). However, the side effects of radiotherapy can be severe, and the trade off between survival and quality of life is important to consider. It was found that the clinical status before radiotherapy was a good indicator of the duration of disability-free life after radiotherapy. The authors concluded that for those already disabled by the tumour, radiotherapy offered little physical gain and even if not severely disabled the treatment could cause severe adverse effects.

Other measures and rates

Other epidemiological measures and rates can be derived, for instance related to childbirth or co-morbidity, and are of importance in certain health care areas:

- *Birth rate* is usually defined as the number of live births per mid-year population;
- *Fertility rate* is usually defined as the number of live births per number of women aged 15–44 years;
- *Infant mortality rate* is defined as the number of infant (<1 year) deaths per number of live births;
- *Stillbirth rate* is defined as the number of intrauterine deaths after 28 weeks per total births;
- *Perinatal mortality rate* is the number of stillbirths + deaths in first week of life per total number of births.

Such epidemiological data can be used to investigate causation and assist prevention, but the issues are often complex.

This is well illustrated in a study of fertility in epilepsy amongst a general population of 2,052,922 persons in England and Wales. Age-specific fertility rates were defined as the number of live births per 1000 women-years at risk, in each age category. Fertility was about 30% lower among women with treated epilepsy, with an overall rate of 47.1 live births per 1000 women aged 15–44 per year (42.3–52.2), compared with a national rate of 62.6 in the same age group. The standardized fertility ratios were significantly lower between the ages of 25 and 39 years in women with epilepsy ($P < 0.001$; Figure 1.3). The reasons for these lower rates are complicated. There are undoubtedly social effects: women with epilepsy have low rates of marriage, marry later, experience social isolation and stigmatization. Some avoid having children because of the risk of epilepsy in the offspring, and some because of the teratogenic potential of anti-epileptic drugs. Other patients have impaired personality or cognitive development. However, there are other biological factors that could lead to reduced fecundity. These include genetic factors and adverse anti-epileptic drug effects. The lowering of fertility is a worrying finding which is another and important source of disadvantage for women with epilepsy. If there are potentially preventable causes, these should be sought.

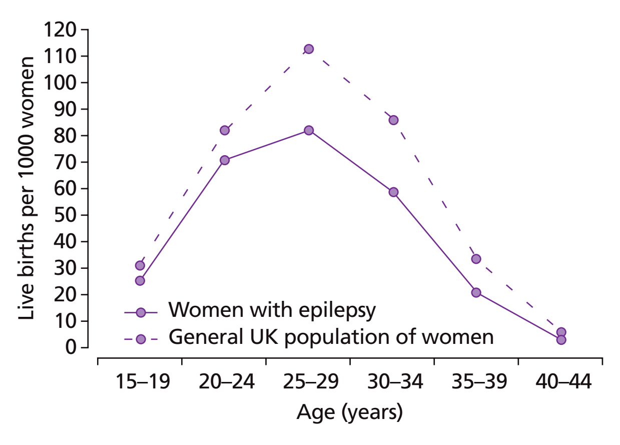


Figure 1.3 Comparison of age-specific fertility rates in women with treated epilepsy and general UK population of women in 1993 (study of a population of 2,052,922 persons). (From Wallace, Shorvon & Tallis (1998), with permission.)

Many neurological conditions have chronic courses, so long-term follow-up is important to our understanding of their prognosis and resource implications. Epidemiologically based prospective cohort studies are the optimal method of study to assess the full impact of the disease.

Burden of illness

Although the study of the epidemiology of disease provides figures on incidence, prevalence, risk factors and distribution within a population, such information is of little practical value unless linked to a treatment (or prevention) programme and resource utilization. A problem that lies at the heart of care provision is the need to focus interventions where needed.

Definitions

The term ‘burden of illness’ in its widest sense incorporates all negative impacts of illness, although is often used to denote the financial costs of illness where costs are understood to encompass the full social costs, both subjective hard to quantify elements as well as objective more easy to quantify measures. These cost of illness studies have the advantage of attempting to quantify a range of negative effects in monetary terms and thus allow comparisons to be drawn. Their disadvantages are obvious – notably the inherent inaccuracies and absurdities of trying to define quality of life issues in terms of monetary loss. Utility measures (e.g. quality-adjusted life years [QALYs] and disability-adjusted life years [DALYs]) have also been derived to try to quantify burden more widely, and a particularly important project has been ‘The Global Burden of Disease’ project sponsored by the WHO and World Bank. The burden of illness on individuals and on carers are not comprehensively accounted for in such studies which focus on broad categories biased towards societal and economic considerations.

Cost of illness studies

The principal concern of physicians is to provide individual care, but as health care costs are rising so fast, and even the richest economies are seeking to limit expenditure, clinicians are necessarily now involved in factoring in economic considerations when making therapeutic decisions. This has led to cost of illness studies, which although important are bedevilled with methodological problems that limit their usefulness.

The perspective taken in the analysis is of primary importance in any study of cost of illness. The cost (and burden) for individuals has quite different parameters to the burden for families, for health services or for society in general. Most cost of illness studies are carried out from the point of view of society, with social costs estimated in terms of lost employment, lost productivity and premature death.

Costs are usually divided into two types: direct and indirect. In outline, the direct costs are defined as any resource utilization required in the care of the illness. These include medical costs such as primary care, hospital out-patient, hospital in-patient, investigation, drugs and non-medical costs such as residential care, community care, training and rehabilitation. Indirect costs are defined as the costs resulting from lost economic production and include premature mortality, dependency, unemployment and underemployment. There are various categories of cost, and any comprehensive analysis should include opportunity costs and transfer payments. Estimation of indirect costs may use the 'human capital' approach which ascribes a monetary value to a person in terms of their potential productivity. In health economic analysis the willingness to pay approach has become popular, which defines costs in terms of how much a person would be willing to spend. This has the advantage of accounting for intangible as well as tangible effects. Both methods are difficult to carry out and both are open to a wide variety of biases and criticisms. With all neurological disorders, the indirect costs are greatly in excess of the direct costs. In one study of epilepsy in 1994, for instance, indirect costs accounted for only 13% of all costs in spite of relatively narrow definition of cost.

There are four common methodologies for carrying out economic appraisal and comparative studies: cost-minimization analysis, which compares interventions where the outcomes are the same; cost-effectiveness analysis, where outcomes are compared using a single natural measure (e.g. in epilepsy, cost per 50% reduction in seizure frequency); cost–utility analysis, which are particularly useful for comparing costs between diseases, in which different outcomes can be accounted for and costs are compared in terms of their effects on a utility measure (e.g. the effect on QALYs); and finally cost–benefit analysis which measures outcome in terms of economic benefit – accounting for both direct and indirect costs. The latter analysis is the most comprehensive, but in neurology there have been few examples of cost–benefit studies. With the increasing availability of expensive therapies and investigations, however, there is a pressing need for good economic appraisal.

WHO burden of illness studies

In recent years, the WHO and World Bank have evolved a more comprehensive series of measures of the impact of disease. The best known are the QALY or the DALY. The DALY uses a methodology that focuses on disability whereas the QALY focuses on quality of life. These were formidable efforts, involving the WHO in 40 person-years of effort and the collection of data on 483 separate sequelae in 107 diseases and 14 million death certificates. It has to be said, as will be quite obvious to all, that reducing the impact of illness into a one-dimensional measure presents difficulties that are as intractable as those of quantifying illness in monetary terms. The Global Burden of Disease study provides comparative statistics on the impact of disease from 107 countries. To what extent this effort is worthwhile, finally, in helping set priorities has been seriously questioned.

The DALY is an indicator that is most useful in making comparisons between diseases and between regions, and in Table 1.6 some comparative figures are shown for neurological and psychiatric disease. On the basis of this analysis, neuropsychiatric disease accounted for about 15% of the global burden of disease (and 34% of the global burden of disability). Cerebrovascular disease accounts for instance for about 10% of the global burden of neuropsychiatric disease, dementia 2% and epilepsy 1%.

The personal burden of neurological disease – stigma

The burden of illness of any neurological disease includes aspects that are less directly related to economic factors. Psychological, social, educational, employment and legislative aspects can have a major impact. Some of these are proportionate and rational (e.g. driving restrictions in epilepsy or stroke) but others are not, and a particular issue for patients with neurological disease is the stigma attached to the disease.

Table 1.6 Disability-adjusted life year (DALY; in thousands) calculations for year 2000 for neurological and psychiatric conditions. Disability-adjusted life year is an indicator of the time lived with a disability and the time lost due to premature mortality. Reproduced with permission from the World Health Organization 1996b.

Condition	DALYs			
	Developed countries*	India	Sub-Saharan Africa	World
Neurological and pychiatric conditions (all)†	24,682	23,949	15,788	165,082
Cerebrovascular disease	5,166	5,223	5,487	45,770
Unipolar depression	6,721	10,064	6,193	60,166
Bipolar disease	1,673	2,867	1,785	16,722
Schizophrenia	2,151	2,041	611	14,614
Epilepsy	427	848	526	4,712
Alcoholism	4,611	1,113	2,387	18,973
Dementia	3,286	1,192	453	10,135
Parkinson's disease	523	167	63	1,278
Multiple sclerosis	222	253	140	1,569

* Defined as 'established market economies'.

† This category excludes cerebrovascular disease.

Stigma deserves special mention, for it is important in many neurological disorders and yet its consequences are overlooked in burden of illness studies. It is often divided into three categories: enacted (actual experience of discrimination), felt (the fear of discrimination) and self (for instance, devaluation or shame or withdrawal as a personal response to perceived discrimination). There are complex interactions and society will often construct a 'stigma theory' about a disease – to explain the dangers the person represents and which imputes a wide range of imperfections on the basis of the disease. The impact of stigma in neurological disease and epilepsy provides an example. The fact of 'being epileptic' is often more devastating than the simple occurrence of occasional epileptic seizures. In 1989, in Britain, felt stigma was found to be nine times less common than enacted stigma. For the patient, epilepsy results in a continuing uncertainty of being interrupted by recurrent attacks which are unpredictable, often dramatic, frighten, horrify or anger onlookers and which are imbued in primitive beliefs about possession and disgust. There results in society a belief that sufferers are retarded, weak, slow, antisocial, physically unattractive or aggressive. Such beliefs are most prevalent in developing societies, but even in the USA in a number of states, up until 1956, people with epilepsy were prohibited from marrying and could be sterilized, and until the 1970s were excluded from restaurants and theatres. In a large study published in 1999 and 2000, amongst more than 5000 persons with epilepsy in Europe, 51% reported feeling stigmatized and 18% highly stigmatized.

The impact of even non-serious illness can be significant. A study from Dunedin of tension headache and migraine showed significantly poorer social, mental, physical and emotional functioning than matched non-headache controls. Although equal numbers of those with and without migraine were in employment, 80% of women with migraine were earning ≤$30,000 or less compared to 67% of controls. Nearly half of those with migraine reported that their headaches impaired their social activities. The burden of disease resulting from migraine was considered equal to that of asthma.

Relative costs – developing countries

Ill health has an economic burden that can impose high and regressive cost burdens on the patient and family in all countries. However, in poorer countries the proportion of family income spent on health may be particularly high, not least as ill health results also in unemployment and underemployment. In Sri Lanka, for instance, where health services are free at the point of delivery, it has nevertheless been estimated that the total cost of all illness amounts to 10% of household incomes, and it is likely that neurological illnesses, because of their generally chronic and disabling nature, are particularly onerous. Tuberculosis (TB) is a serious chronic illness which has been well studied from the health economic point of view. In Thailand, it has been reported that TB results in 15% of poor households having to sell material property and 10% taking out loans. In India, amongst patients with TB, 67% of rural patients and 75% of urban patients incurred TB-related debts. Eleven per cent of school children with parents with TB had to discontinue their studies and another 8% had to take up employment. What applies to TB will no doubt also apply to chronic neurological diseases. The impact of diseases depends primarily on the economic position of the family (the lower the economic status, the greater the impact) and the social or family networks and community support available.

Treatment gap

It is also largely economic factors that lie at the heart of failure of treatment. Taking the example of epilepsy again, in 1989, Shorvon and colleagues coined the phrase 'epilepsy treatment gap' to provide a numerical measure of the extent of failure of therapy. The treatment gap was defined as the percentage of patients with active epilepsy in a population who do not receive anti-epileptic drugs. It is a simple estimate based on prevalence and drug supply figures for that country, and assumes standard low dose monotherapy. Surprising and disturbing results were obtained – in Pakistan, the Philippines and Ecuador treatment gaps of 94%, 94% and 80%, respectively, were ascertained. Although estimates, we considered these to be underestimates if anything (resulting from low estimates of prevalence and assumptions of low drug dosages). Since then, prospective population-based studies have largely confirmed these findings, with 62% treatment gap ascertained, for instance, in China and 73–78% in India. Another study has shown that 41% of people with epilepsy in China have never received anti-epileptic drugs. There are various reasons for these deficiencies of treatment including cost, availability (not least the availability of drugs in pharmacies), cultural factors, lack of medical facilities, and lack of understanding of the potential and role of therapy. Closing the 'treatment gap' has become a priority for health services in many countries, and these findings were a primary stimulus for the highly successful joint WHO and the International League Against Epilepsy (ILAE) campaign to improve epilepsy care – *The Global Campaign Against Epilepsy.* The campaign is one example of how epidemiological data can be translated into societal action, and the results of the campaign interventions using improving treatment gap statistics are currently under evaluation.

Certain topics of interest have had to be omitted from this necessarily brief survey of 'The burden of neurological illness worldwide'. Amongst these, prevention is not mentioned, although the prevention of neurological disease has not been well studied generally. In most countries of the world, even basic epidemiological data on many, particularly uncommon, neurological disorders has not been calculated. Ethical issues are also important in this area but are not covered here, especially in relation to resource utilization. For instance, as doctors, our primary responsibility is to the individual patient and not society. Therapies which are not 'cost' effective' from the epidemiological or societal point of view, may be nevertheless beneficial in an individual – and here the societal and clinical perspectives may clash (although cultures that purport to put society before the individual usually apply hypocritically different standards to the rulers and the ruled). The impact of social policy, for instance in relation to financial benefits and social support, on the burden of illness has also not been touched upon, although it can greatly influence the individual burden.

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2 Nervous System Structure and Function

Charles Clarke, Roger Lemon

BASIC NEUROSCIENCE

Introduction

The complexity of the nervous system posed daunting challenges for clinical neurology as the discipline emerged from the late 19th century into the early 20th. However, despite the truly remarkable description of the intricacies of axonal and dendritic networks by Cajal in the 1890s, using the light microscope (Figures 2.1 and 2.2), the cortical mapping by Brodmann and later the fine detail of neuro-anatomical pathways by Brodal and many others in the 1940s, it remained entirely evident that a distinctly rudimentary knowledge of neuro-anatomy – and little of physiology – was all that was necessary to provide a robust basis for most day-to-day neurological practice. It is also something of an enigma that neurologists training in the 21st century continue to use basic clinical tools from over 100 years ago; many neurologists in the past have had a relatively sketchy knowledge of pathways, physiology and mechanisms – although this is an indication of the reliability of simple observation of symptoms and signs in day-to-day practice.

But times are changing fast. Advances in imaging, neurogenetics, neurochemistry, neurotransmitter technology, immunology and molecular biology have added entirely new dimensions to clinical practice, to the relevance of neuronal and glial ultrastructure and function and complexities of neuro-anatomy. We now begin by looking at ultrastructure, functional imaging, genetics, chemistry and neuronal activity to understand conditions as diverse as Alzheimer's disease, Parkinson's disease, myasthenia gravis, polyneuropathies and recurrent headache – itself the most common neurological complaint the world over and of major economic importance. This chapter provides a brief overview of how the nervous system is organized and, where appropriate, how abnormalities found on examination are explained, both anatomically and neurochemically.

The functional unit: the neurone

The neurone (>100 billion within the human brain) is the functional unit of the nervous system. Neuronal specificity, size and cell type vary greatly. One α-motor neurone of the lumbar cord has an axon over 1 m in length and innervates between several hundred and 2000 muscle fibres – to form a motor unit. By comparison, some spinal or intracerebral interneurones have axons under 100 μm long which terminate on a single neuronal cell body. A summary of neuronal ultrastructure follows.

The neurone is constituted by its nucleus, cytoplasm, neuronal membrane and cytoskeleton (Figure 2.3). Neurotransmission and intrinsic modification of the neurone itself are its functions – to facilitate transfer of information, to adapt to and record change. The combination of axonal electrical activity and synaptic neurotransmitter release provides the basis for most interneuronal transmission, with an important role also for the release of neuromodulators. The integrity of intraneuronal and glial structure and function is also essential; glia are now known to play a part in synaptic transmission, re-uptake of neurotransmitters and the general control of the extracellular environment in which the neurones are located. Neuronal plasticity indicates the ability of neurones to adapt, to change, singly, in sequence and/or in groups and is a particularly well-developed aspect of the mammalian nervous system. Plasticity has a pivotal role in both learning and recovery from injury, and can involve changes in all or any part of the neurone.

From the neurone cell body (soma, perikaryon) extend neurites, i.e. axons (up to 1 m long) and dendrites (rarely longer than a few millimetres). Most axons branch repeatedly to establish synaptic connections with other neuronal cell bodies. In this way neurones are able to make divergent connections with many other neurones within the CNS.

Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

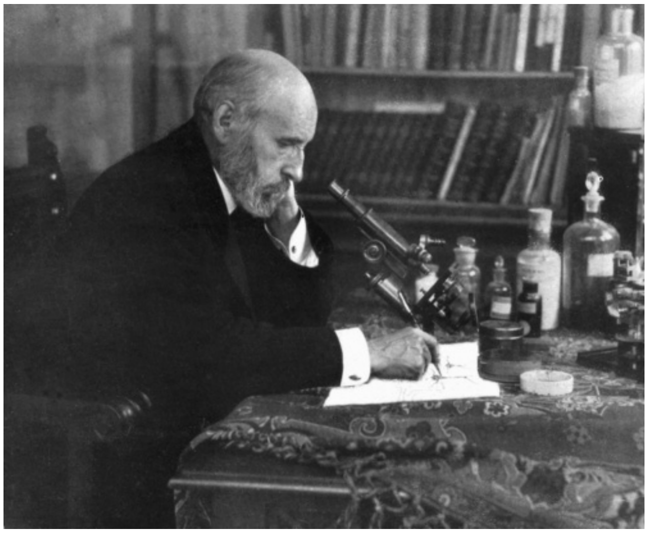


Figure 2.1 Santiago Ramón y Cajal (1852–1934) with his light microscope in 1915. (*With kind permission of the Instituto Cajal*, Madrid.)

The dendritic and soma membrane represents the main region through which the neurone receives its synaptic input. Some neurones receive many thousands or even hundreds of thousands of such inputs. The neuronal membrane is the 5 nm thick barrier enclosing cytoplasm, excluding substances bathing the neurone. This membrane bilayer of phospholipid has typically a polar hydrophilic head and an insoluble non-polar hydrophobic tail. Neuronal membrane proteins are responsible for the interaction between the neurone and its environment. These proteins are:

- Ion channels, usually either ligand-gated or transmitter-gated;
- Receptors; and
- Cell adhesion molecules.

The cytoskeleton consists of microtubules, neurofilaments and microfilaments. Microtubules are some 20 nm diameter, hollow-walled strands of α and β tubulin – polymers of globular microtubule associated proteins (MAPs). Tau is an axonal MAP. Dynein and kinesin are motor proteins (aka molecular motor or motor molecules) that convert chemical energy in ATP into mechanical energy (movement).

Neurofilaments are 10 nm thick (intermediate filaments of all other cells), braided, tight, physically strong protein strands. They form a peri-nuclear network and provide structural integrity. Microfilaments are 5 nm thick, braided duplexes of actin (42–44 kDa). They are critically involved in neurone shape, where they have a role analogous to those in muscle.

Neuronal replication is the exception, although neurogenesis has been clearly shown to take place in the olfactory neuroepithelium, hippocampus and hypothalamus. Neuronal dynamics imply that intraneuronal contents are continually being reformed and degraded. The cofactor ubiquitin molecule interacts with degraded proteins via hydrophobic residues – complexes of more than five ubiquitin molecules are broken down by an ATP-dependent multi-enzyme system, the 26S proteasome. Failure to remove degraded proteins is of signal importance in many neurodegenerative diseases (e.g. Alzheimer's disease; Chapter 7), and myopathies such as inclusion body myopathy (Chapter 9).

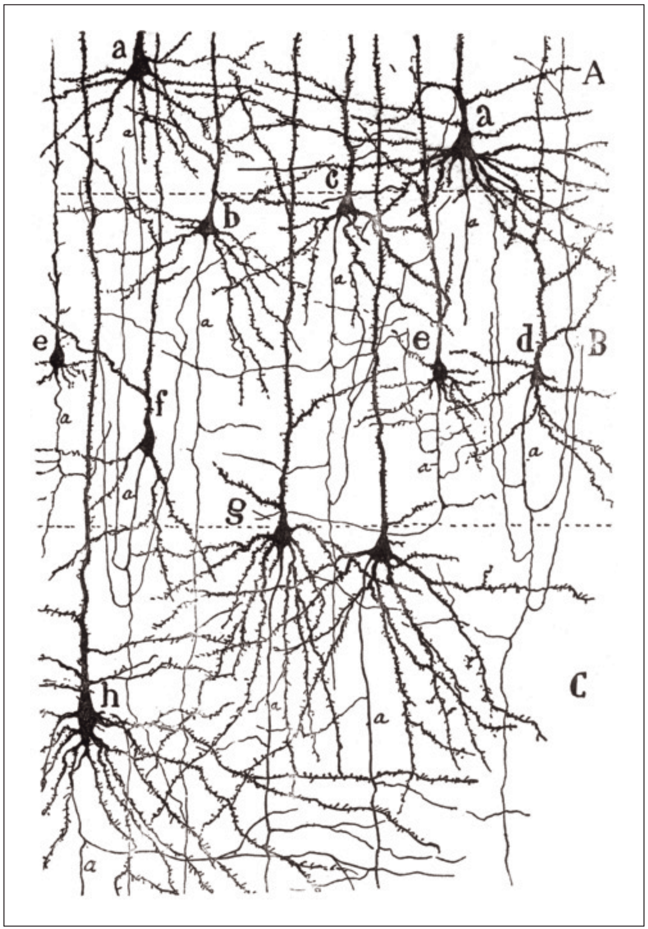


Figure 2.2 Fine detail of cortical neuronal networks (Cajal). First, second and third layers of precentral gyrus of the cerebrum. A, B, C, small pyramidal cells; D, E, medium pyramidal cells; F, G, H, bitufted cells and dendritic shafts. (*With kind permission of the Instituto Cajal*, Madrid.)

Amyloid and tau in degenerative brain diseases

Any detailed account of normal and pathological neurochemistry is far outside the scope of this chapter. However, it is relevant to include here a synopsis of some neurochemical findings in common degenerative neuronal diseases, especially Alzheimer's (Chapter 7).

In Alzheimer's disease, neurofibrillary tangles develop – filamentous inclusions within the soma and dendrites adjacent to it. Paired helical and 15 nm straight insoluble protein filaments become visible. These are isoforms of tau, the microtubule binding protein that in health is soluble. This structural change in the cytoskeleton is likely to impair axonal transport, neurotransmission and eventually viability of the neurone.

In the second pathological hallmark of Alzheimer's, the extracellular senile plaque, deposits of amyloid are surrounded by dystrophic neuronal elements. Amyloid is the name given to

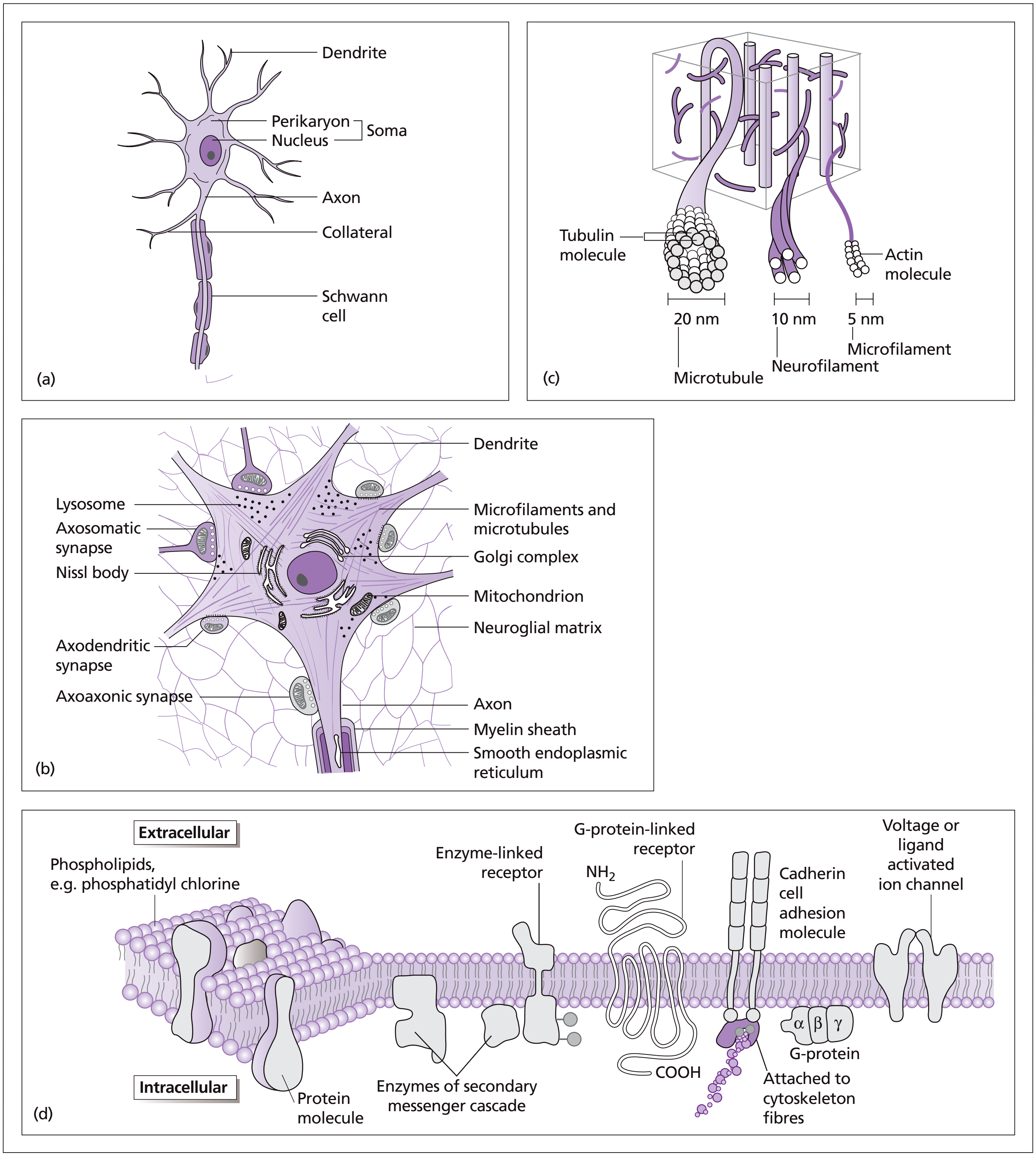

Dendrite
Perikaryon
Nucleus
Soma
Axon
Collateral
Schwann cell
(a)
Tubulin molecule
Actin molecule
20 nm
10 nm
5 nm
Microfilament
Neurofilament
Microtubule
(c)
Dendrite
Lysosome
Axosomatic synapse
Nissl body
Microfilaments and microtubules
Golgi complex
Mitochondrion
Neuroglial matrix
Axodendritic synapse
Axoaxonic synapse
Axon
Myelin sheath
Smooth endoplasmic reticulum
(b)
Extracellular
Phospholipids, e.g. phosphatidyl chlorine
Enzyme-linked receptor
G-protein-linked receptor
NH2
Cadherin cell adhesion molecule
Voltage or ligand activated ion channel
α β γ
G-protein
COOH
Attached to cytoskeleton fibres
Enzymes of secondary messenger cascade
Protein molecule
Intracellular
(d)

Figure 2.3 Motor neurone. (a) Soma, axon and Schwann cell; (b) ultrastructure; (c) cytoskeleton; (d) neuronal membrane.

β-pleated sheets of aggregates of fibrillar peptides that stain with Congo red and are doubly refractive in polarized light. Aβ amyloid, a 4 kDa peptide cleaved from amyloid precursor protein (APP) is the main constituent of histological amyloid.

APP is one member of a larger family of amyloid precursor-like proteins, APLP1 and APLP2. APP is encoded by a gene in the long arm of chromosome 21; it exists in three main isoforms of 695–770 aminoacids. Neuronal APP is the source of most extracellular Aβ amyloid in Alzheimer's disease. APP synthesis takes place in the rough endoplasmic reticulum. It is glycosylated in the Golgi apparatus and offered to the surface of the neurone as an integrated membrane protein. A fraction of APP within the plasmalemma remains within the neurone from which are generated various forms of Aβ ($A\beta_{1-40}$, $A\beta_{1-42}$, truncated $A\beta_{17-40}$ peptides). Putative mechanisms of neurotoxicity of Aβ fragments and the genetics of Alzheimer–APP gene mutations (chromosome 21), presenilin 1 and 2 (chromosomes 14 and 1), and allelic forms of ApoE (chromosome 19) are discussed in Chapter 7.

Neurotransmission

Electrical synapses

Between mammalian neurones, electrical synapses, found, for example, in the giant squid, have largely been replaced by chemical transmission systems. Evolutionarily distant electrical synapses still occur at gap junctions, where the synaptic cleft is some 3 nm wide. Connexin protein complexes (see Myelin below) span these narrow gaps, coupling adjacent cells electrotonically with pores some 2 nm in diameter. These pores are large enough for the passage of all major cellular ions and many organic molecules. Electrical transmission is bi-directional, and slow. Gap junctions are seen in mammalian glial cells, epithelial cells, smooth and cardiac muscle cells, and in some nuclei in the brain, e.g. the inferior olivary nucleus. There is evidence that during brain development, transmission via gap junctions between neighbouring neurones coordinates growth and maturation.

Chemical synapses

In a chemical synapse, the synaptic cleft is some 20–50 nm wide and filled with an adherent matrix, ensuring its stability. The presynaptic element, usually an axon terminal, houses mitochondria, synaptic vesicles and larger secretory granules – the dense-core vesicles seen on electron microscopy (EM). Either side of the synaptic cleft specialized areas of accumulated protein comprise membrane differentiations, with an active zone on the presynaptic side opposite the post-synaptic density. The post-synaptic density houses receptors. Receptors make possible intracellular events, a change in membrane potential or secondary chemical events. Receptors are specially sensitive to interaction with neurotransmitters and neuromodulatory agents released by the presynaptic neurone.

Types of CNS synapse

CNS synapses are classified as axodendritic (axon → dendrite), axosomatic (axon → cell body), axo-axonic and dendrodendritic. The terms Gray's Type I and II synapses are also used (Figure 2.4):

- *Gray's Type I*: asymmetrical, post-synaptic membrane differentiation thicker and more complex than presynaptic, usually excitatory;

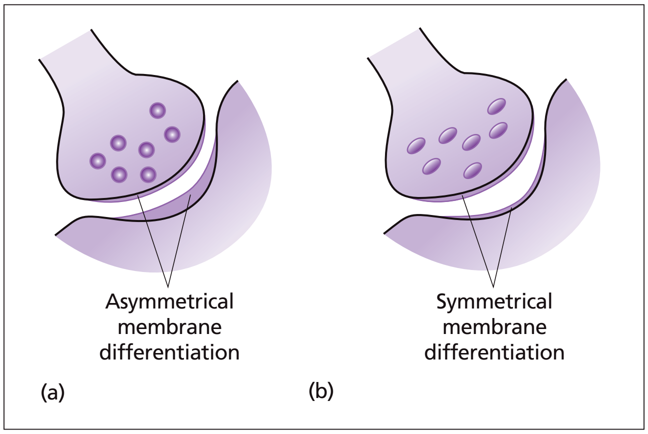

Asymmetrical membrane differentiation
Symmetrical membrane differentiation
(a)
(b)

Figure 2.4 Types of synapse. (a) Gray's Type I: asymmetrical, typically excitatory; (b) Gray's Type II: symmetrical, typically inhibitory.

- *Gray's Type II*: symmetrical membrane differentiation, similar thickness, usually inhibitory.

Peripheral nervous system synapses

Synaptic transmission is involved in communication throughout the peripheral nervous system (PNS), including transmission from motor nerves to striated skeletal muscle fibres and from autonomic fibres to smooth and cardiac muscle. The skeletal neuromuscular junction is a specialized cholinergic synapse facilitating fast reliable neuromuscular transmission. Its peripheral site and accessible micro-anatomy has made possible a detailed study of its function in health and disease.

Neuromuscular junction

At the motor end-plate presynaptic active zones are closely aligned to the post-synaptic membrane densely packed with acetylcholine receptor sites (Figure 2.5). Acetylcholine, liberated by an action potential leads to acetylcholine release from synaptic vesicles into the synaptic cleft. Depolarization of the motor end-plate follows.

Neurotransmitters

Effective chemically mediated synaptic transmission requires transmitters to be synthesized, transported, liberated appropriately and metabolized or recycled. Neurotransmitters fall into one of four categories (Table 2.1).

Neurotransmitters are synthesized in several ways. Glutamate and glycine are ubiquitous amino acids, abundant in all cells including neurones. GABA and amine neurotransmitters are made only by neurones that release them, via specific enzymes and precursors. Synthesizing enzymes for both amino acid and amine neurotransmitters are transported to the axon terminal where they direct transmitter synthesis, locally and promptly.

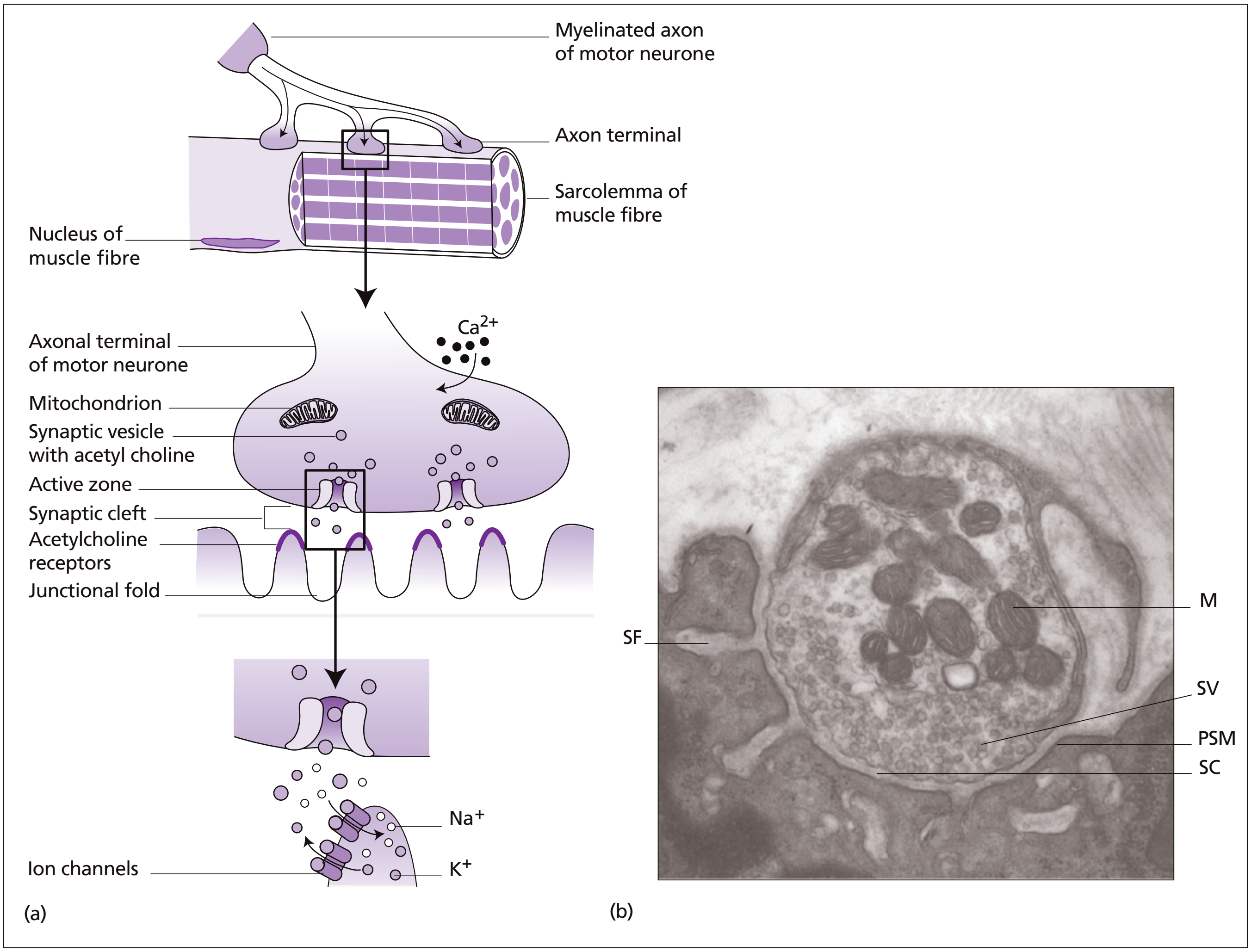

Myelinated axon of motor neurone
Axon terminal
Sarcolemma of muscle fibre
Nucleus of muscle fibre
Axonal terminal of motor neurone
Ca^{2+}
Mitochondrion
Synaptic vesicle with acetyl choline
Active zone
Synaptic cleft
Acetylcholine receptors
Junctional fold
Na+
K+
Ion channels
(a)
SF
M
SV
PSM
SC
(b)

Figure 2.5 Neuromuscular junction. (a) General arrangement and detail. (b) Electron micrograph of a neuromuscular junction from mouse flexor digitorum brevis muscle. M, mitochondrion; PSM, postsynaptic membrane; SC, synaptic cleft; SF, synaptic fold; SV, synaptic vesicle. Courtesy of Dr Tom Gillingwater, Centre for Integrative Physiology, University of Edinburgh. From Gillingwater TH, Ribchester RR. Compartmental neurodegeneration and synaptic plasticity in the Wlds mutant mouse. *J Physiol* 2001; 534: 627–39 with permission.

Table 2.1 Principal neurotransmitters.

Amino acids	**Amines**	**Peptides (many others)**	**Gases**
γ-Amino-butyric acid (GABA)	Acetylcholine (ACh)	Cholecystikinin (CCK)	Nitric oxide (NO)
Glutamate (Glu)	Dopamine (DA)	Dynorphin	Carbon monoxide [?] (CO)
Glycine (Gly)	Adrenaline (epinephrine)	Enkephalins (Enk)	
	Noradrenaline (norepinephrine)	*N*-acetyl-aspartyl-glutamate (NAAG)	
	Histamine	Neuropeptide Y	
	Serotonin (5-HT)	Somatostatin	
		Substance P	
		Thyrotropin-releasing hormone (TRH)	
		Vasoactive intestinal peptide (VIP)	

Purines, ATP and adenosine are also neurotransmitters.

Once synthesized, transporter proteins concentrate amino acid and amine transmitters within synaptic vesicles.

Peptide neurotransmitters are strung together by ribosomes within the rough endoplasmic reticulum (ER) and cleaved to form active molecules in the Golgi apparatus (GA). Secretory granules bud off the GA and are carried to the axon terminal by axoplasmic transport.

Amine and amino acid transmitters are stored in and released from synaptic vesicles. Peptide neurotransmitters are stored in and released from secretory granules. These may coexist in the same neurone, to be released under different conditions.

Transmitter release

Neurotransmitter release into the synaptic cleft is triggered by the arrival of an action potential at the axon terminal, where depolarization of the terminal membrane causes voltage-gated calcium channels to open. Vesicles release transmitters by exocytosis at an active zone into the synaptic cleft; the vesicle membrane is recovered by endocytosis.

Secretory granules (dense core vesicles) also release neurotransmitters by exocytosis, but typically not at active zones. Peptide neurotransmitters are not released by every action potential, but typically by high frequency trains of action potentials. Peptide release is typically slow (50 ms), while amino acid and amine release is rapid.

Transmitter-gated ion channels and G-protein-coupled receptors

Neurotransmitter–receptor binding – a key–lock analogy is simple but valuable – alters the shape of receptor protein and hence its function. There are two distinct types of receptor. Transmitter-gated ion channels consist of protein subunits that open an ion pore, and change shape in response to neurotransmitter. For example, the ACh-gated ion channel at the neuromuscular junction, permeable to both Na^+ and K^+, is triggered to produce an excitatory post-synaptic potential (EPSP) in response to ACh. Both ACh and glutamate-gated channels trigger EPSPs when activated, i.e. are excitatory. Glycine-gated and GABA-gated channels, permeable to Cl^- ions and tending to hyperpolarize the resting membrane potential, are inhibitory, triggering inhibitory post-synaptic potentials (IPSPs). Amino-acid and amine neurotransmitters deliver fast synaptic transmission via transmitter-gated ion channels.

G-protein-coupled receptors are involved in a more diverse, slower and longer lasting mechanism of chemical synaptic transmission in response to amino-acid, amine and peptide neurotransmitters. Receptor proteins activate G-proteins that travel along the intracellular face of the post-synaptic membrane. These in turn activate effector proteins – membrane-located G-protein-gated ion channels or enzymes that synthesize second messengers.

Glia

Within the CNS, four types of glial cells support neuronal activity: astrocytes, oligodendrocytes, microglia and ependymal cells. Schwann cells are the neuroglia of the PNS, investing certain peripheral axons with myelin. Neurones are biologically dependent upon glia.

Astrocytes

These are microscopically star-shaped shaggy cells from which protrude several dozen, fine astroglial processes that make intimate contact with neurones (Plate 2.1). Intermediate filaments within astrocyte cytoplasm lend tensile strength to the brain and cord. Glycogen granules within astrocyte cytoplasm provide intermediate energy (glucose) to surrounding neurones. Astrocytes are engaged in recycling glutamate and GABA and scavenging K^+ ions following neurotransmission; they have an essential role in controlling the composition of the extracellular fluid. Glial limiting membranes – from astrocytic processes – cover the pial surface of the brain and with ependyma line the ventricles. Vascular processes of astrocytes are in intimate contact with CNS capillaries. Astrocytes retain a capacity to multiply throughout life, and do so following neuronal injury to form glial scars (gliosis). Neoplastic proliferation leads to astrocytomas (Chapter 20).

Oligodendrocytes (oligodendroglia)

One oligodendrocyte lays the myelin sheaths of 30–40 CNS axons, the inner and outer surfaces forming the spiral sheaths seen as minor and major dense lines on microscopy. The axon is exposed between oligodendroglial segments at each node of Ranvier. Paranodal pockets – collections of cytoplasm – are visible at each end of each myelin lamination (see Schwann cells below).

CNS myelination commences *in utero* and continues for some 20 years in humans. The effect of the ensheathing myelin lamellar spiral is to facilitate both saltatory conduction and axonal integrity. The nature of CNS demyelination, i.e. the breakdown of normal rapid axonal saltatory conduction, seen typically in multiple sclerosis, is discussed in Chapter 10. Neoplastic proliferation leads to oligodendrogliomas (Chapter 20). Within grey matter, modified oligodendroglia are seen as satellite cells – involved in interneuronal ion transfer. Many CNS axons remain unmyelinated – typically small $<0.2\ \mu m$ diameter fibres.

Microglia

Some cells of neuro-epithelial lineage develop into phagocytes, known as microglia. When stimulated by neuronal injury, demyelination or vascular CNS damage, microglia increase in size to become motile scavengers.

Ependyma

Ependyma are ciliated cells that line the cerebral ventricles and central cavity of the cord, together with astrocytic glial limiting membrane. Their function is to define the integrity of the parenchyma–CSF interface. Ependymal cilia are involved in CSF propulsion. Neoplastic proliferation produces ependymomas (Chapter 20).

Schwann cells

A sequence of Schwann cells ensheaths each myelinated axon of a peripheral neurone. Like CNS oligodendroglial sheaths, ultrastructural major and minor dense lines are seen, and paranodal sockets of cytoplasm at the end of each Schwann cell, recognized by Ranvier in the 1880s. The mesaxon is the mesenteric membrane, displaced centrifugally as the spiral layering of the Schwann cell develops (Figure 2.6). One main function of the Schwann cell is to make possible saltatory conduction. Modified Schwann cells, known as satellite cells, are found within posterior root ganglia and those known as teloglia at enclosed peripheral sensory nerve endings.

Myelination is an active lifelong process. Remyelination is the response to peripheral nerve injury. The effects and mechanisms of peripheral nerve demyelination are discussed further in Chapter 9.

Peripheral nerve fibre types

The complex classification (Table 2.2) of fibre types, assembled largely from mammalian data, is seldom used in clinical practice, but it is of distinct value when a particular fibre type is studied. In the cat conduction velocity up to 15 m/s is achieved in unmyelinated fibres and up to about 120 m/s in myelinated fibres; there is much variation between species. Afferent fibres are classified on a numerical system I–IV, while the A–C classification includes mixed nerves. Peripheral nerve ultrastructure is outlined in Figure 2.6; pathological features are discussed in Chapter 9.

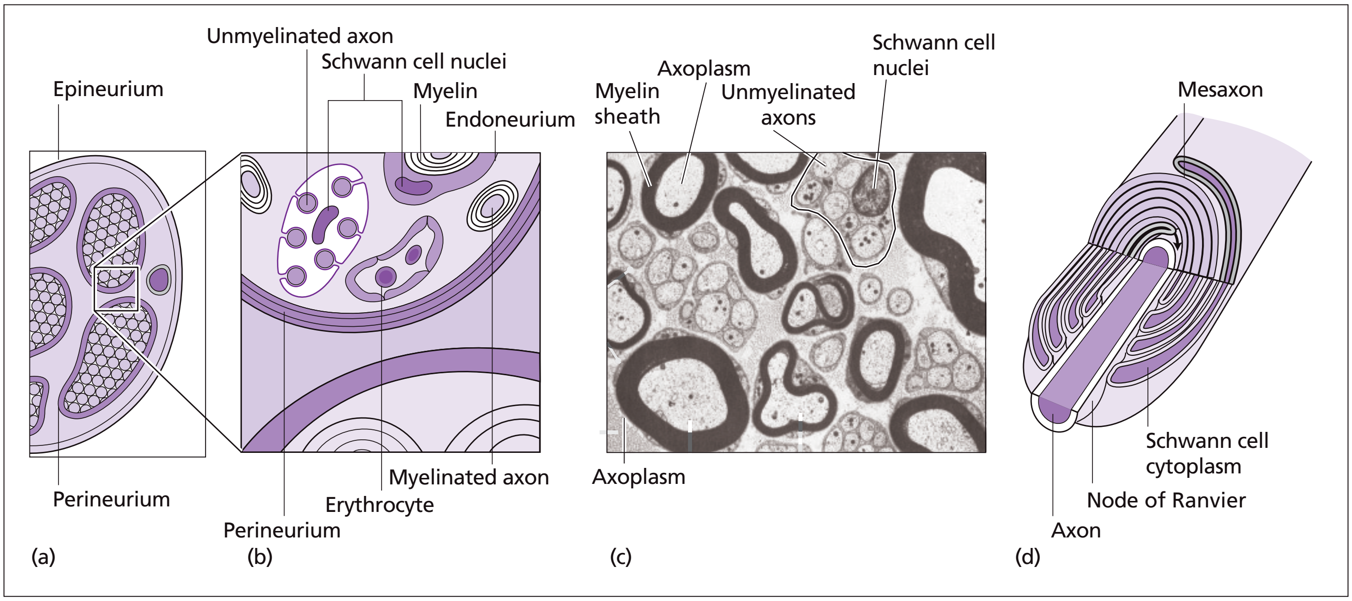


Figure 2.6 Peripheral nerve and Schwann cells. (a) Nerve trunk (transverse section). (b) Detail of (a). (c) Electron micrograph of Schwann cells and axons (courtesy of Professor Sebastian Brandner, Istitute of Neurology). (d) Spiral myelin sheath of Schwann cell.

Table 2.2 Fibre types within peripheral nerves from various mammalian data.

Fibre type	Diameter (µm)	Conduction velocity m/sec	Function
Aα (mixed)	13–22	17–120	α-motor neurones, muscle spindle primary endings, Golgi tendon organs, touch
Aβ (mixed)	8–13	40–70	Touch, muscle spindle secondary endings, joint position
Aγ (mixed)	4–8	15–40	Touch, pressure, γ-motor neurones
Aδ (mixed)	1–4	5–15	Pain, crude touch, pressure, temperature
B (mixed)	1–3	3–14	Preganglionic autonomic
C (mixed)	0.1–1	0.2–3	Pain, touch, pressure, temperature, postganglionic autonomic
Ia (afferent)	12–20	70–120	Muscle spindle primary endings
Ib (afferent)	11–19	66–120	Golgi tendon organs
II (afferent)	5–12	2–50	Touch, muscle spindle secondary endings
III (afferent)	1–5	4–20	Pain, pressure, temperature, crude touch
IV (afferent)	0.1–2	0.2–3	Pain, touch, pressure, temperature

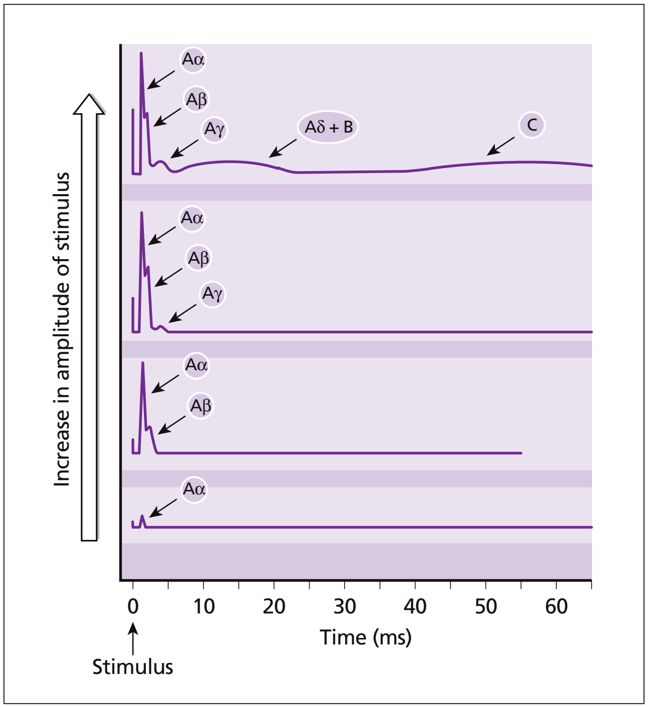


Figure 2.7 Recruitment of nerve fibre types with increasing stimuli. Responses from a typical mixed (motor and sensory) nerve, e.g. sciatic.

Myelin and saltatory conduction

The degree of myelination and fibre diameter are the principal factors determining conduction velocity. The contribution of each nerve fibre type to a compound action potential is outlined above (Figure 2.7). In disease, it will be appreciated that mechanisms that alter nerve function are divided broadly into axonal, i.e. those that affect the axon itself, and demyelinating, where the intregrity of myelin is compromised.

Myelin was a word coined by Virchow, simply for a fatty substance obtained from various tissues; it was adopted by Schwann to describe the 'white substance' of peripheral nerves. CNS myelin provides similar conduction properties, but there are specific neurochemical characteristics that differentiate it from peripheral nerve myelin. Some functional and structural features of peripheral nerve myelin are outlined here:

- Rapid conduction along both peripheral nerves and within the CNS is achieved by saltatory conduction.
- In the myelinated nerve fibre the axonal membrane is adapted at regular sites. Of note, at each node of Ranvier voltage-gated sodium channels are concentrated; these are involved in action potential propagation. Fast and slow potassium channels are involved in membrane repolarisation.
- Depolarization of the axonal membrane at each node of Ranvier is induced by an initial influx of Na^+ ions, leading to a voltage-dependent massive influx of more Na^+ ions, and a new wave of depolarization to be propagated in saltatory fashion (i.e. jumping) to the next node of Ranvier.

Table 2.3 Myelin protein characteristics.

Glycoproteins	Approx %*	Mass (kDa)	Chromosome[†]
P0	65	28	1
PMP22	4	22	17
MAG	1	100	19
Periaxin	5	170	7 (mouse)
E-cadherin	<0.5	130	16
Basic proteins			
MBP	10	14–21.5	18
P2	5	14.8	8
Other proteins			
CNP	<0.5	46/48	17
PLP/DM20	<0.5	30/25	X
Cx32	<0.5	32	X

* Of myelin proteins.
[†] In humans.

- Depolarization is also achieved in unmyelinated fibres, but by sodium channels distributed along the whole length of the axon.

Myelin saves space and conserves energy – to achieve a given mean conduction velocity an unmyelinated axon would require a diameter some 40 times greater than a myelinated one and it would consume 5000 times more energy.

Composition of the myelin sheath

Peripheral myelin is the differentiated plasma membrane of a Schwann cell. It is a lipid-rich, tightly packed spiral surrounding the axon (Figure 2.6) penetrated by cytoplasmic channels (Schmidt–Lanterman incisures).

Gene cloning of the principal myelin proteins and their association with specific neuropathies has thrown light on their role in myelin formation and maintenance. Some basic features of these proteins are outlined in Table 2.3.

Glycoproteins

Protein zero (P0). P0, a major protein of PNS myelin is expressed in all myelinating Schwann cells. The role of the P0 molecule is cell adhesion, promoting and maintaining tight compaction of myelin. One of its domains contributes to the intraperiod line.

Peripheral myelin protein 22 (PMP22). This is probably also concerned with adhesion between lipid and protein molecules. PMP22 is also found widely outside the PNS.

Myelin associated glycoprotein (MAG). MAG is believed to participate in signal transduction during glial differentiation, axonal recognition, adhesion and neurite outgrowth. MAG is located in the Schmidt–Lanterman incisures, paranodal loops at nodes of Ranvier, in external and internal mesaxons and the peri-axonal Schwann cell membrane itself.

Periaxin. The primary localization of this PNS-specific myelin protein is close to the peri-axonal membrane (rather than an integral membrane protein; cf. P0, MAG and PMP22).

Epithelial cadherin (E-cadherin). Cadherins are calcium-dependent adhesion proteins. In Schwann cells, E-cadherin is the major adhesive glycoprotein in non-compacted regions of the myelin sheath.

Basic proteins

Myelin basic proteins

Both CNS and PNS contain peripheral membrane polypeptides known as myelin basic proteins (MBPs). MBPs are believed to participate with P0 in the major dense line and compaction.

Protein P2

P2 is a fatty acid-binding protein, with postulated roles in the assembly, maintenance and remodelling of myelin.

Other proteins

Cyclic nucleotide phosphodiesterases (CNPs) are concentrated in the outer perimeter of the myelin sheath, the outer mesaxon, Schwann cell surface membrane and peri-axonal region.

Proteolipid proteins (PLPs) are localized in compact myelin and thought to have a structural role in the intraperiod line.

Connexin 32 (Cx32) is a component of gap junction channels. It is found at paranodal regions and at Schmidt–Lanterman incisures.

Myelination and axon–Schwann cell interactions

In a developing nerve, a bundle of naked axons is surrounded by a single Schwann cell layer. Schwann cell–axon contact triggers Schwann cell proliferation. The axons become segregated and as maturation continues a one-to-one relationship develops – each Schwann cell investing a single axonal segment. The Schwann cell elongates and rotates as myelin develops about the axis of the axon, to form the nodal spiral structure seen on microscopy.

The precise nature of the axonal signal for myelination remains obscure. However, when Schwann cells receive the signal to myelinate, various transcription factors (Oct-6, Krox-20, Sox-10) participate in gene expression to ensure the particular myelinating phenotype of the individual Schwann cell.

Sensory nerve endings

A single nerve fibre has the same kind of endings on all its terminals, comprising a physiological sensory unit, receiving information from a receptive field. In the skin, each receptive field covers some 5 mm^2 on a finger tip and 2 cm^2 on the upper arm. Sensory units of different modalities frequently supply the same patch of skin (Figures 2.8 and 2.9).

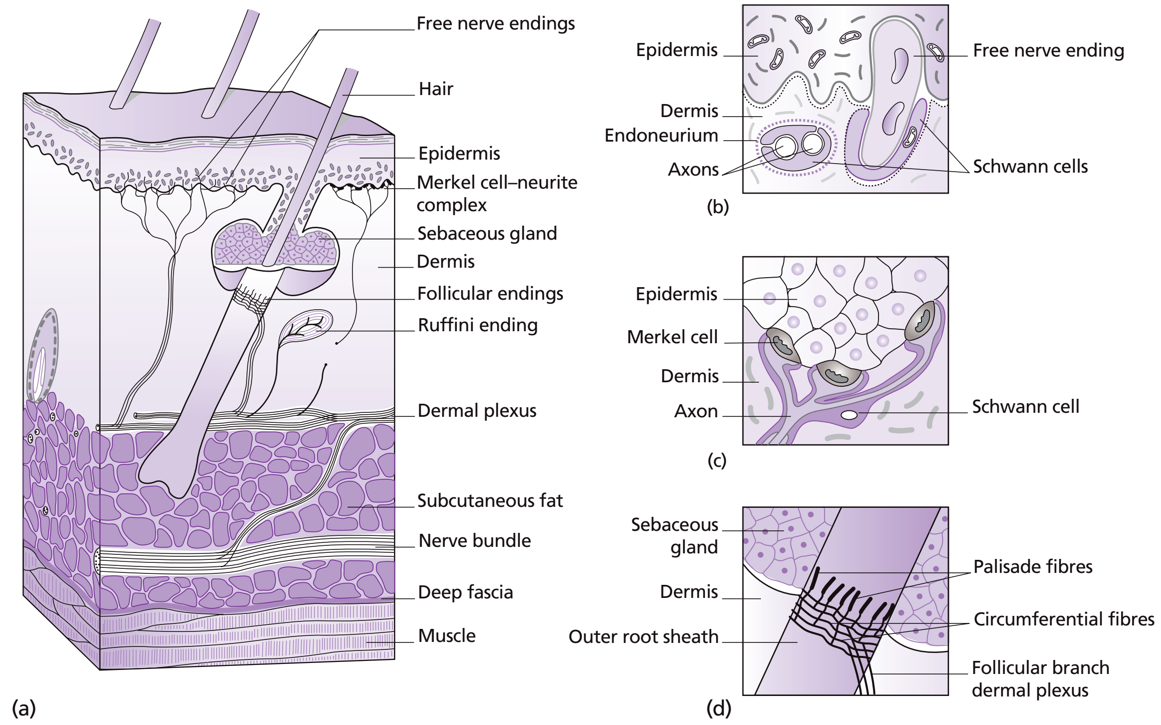

Free nerve endings
Hair
Epidermis
Merkel cell–neurite complex
Sebaceous gland
Dermis
Follicular endings
Ruffini ending
Dermal plexus
Subcutaneous fat
Nerve bundle
Deep fascia
Muscle
(a)
Epidermis
Dermis
Endoneurium
Axons
Free nerve ending
Schwann cells
(b)
Epidermis
Merkel cell
Dermis
Axon
Schwann cell
(c)
Sebaceous gland
Dermis
Outer root sheath
Palisade fibres
Circumferential fibres
Follicular branch dermal plexus
(d)

Figure 2.8 Three examples of nerve endings in hairy skin. (a) General arrangement. (b) Free nerve endings. (c) Merkel cell–neurite complex. (d) Palisade and circumferential nerve endings.

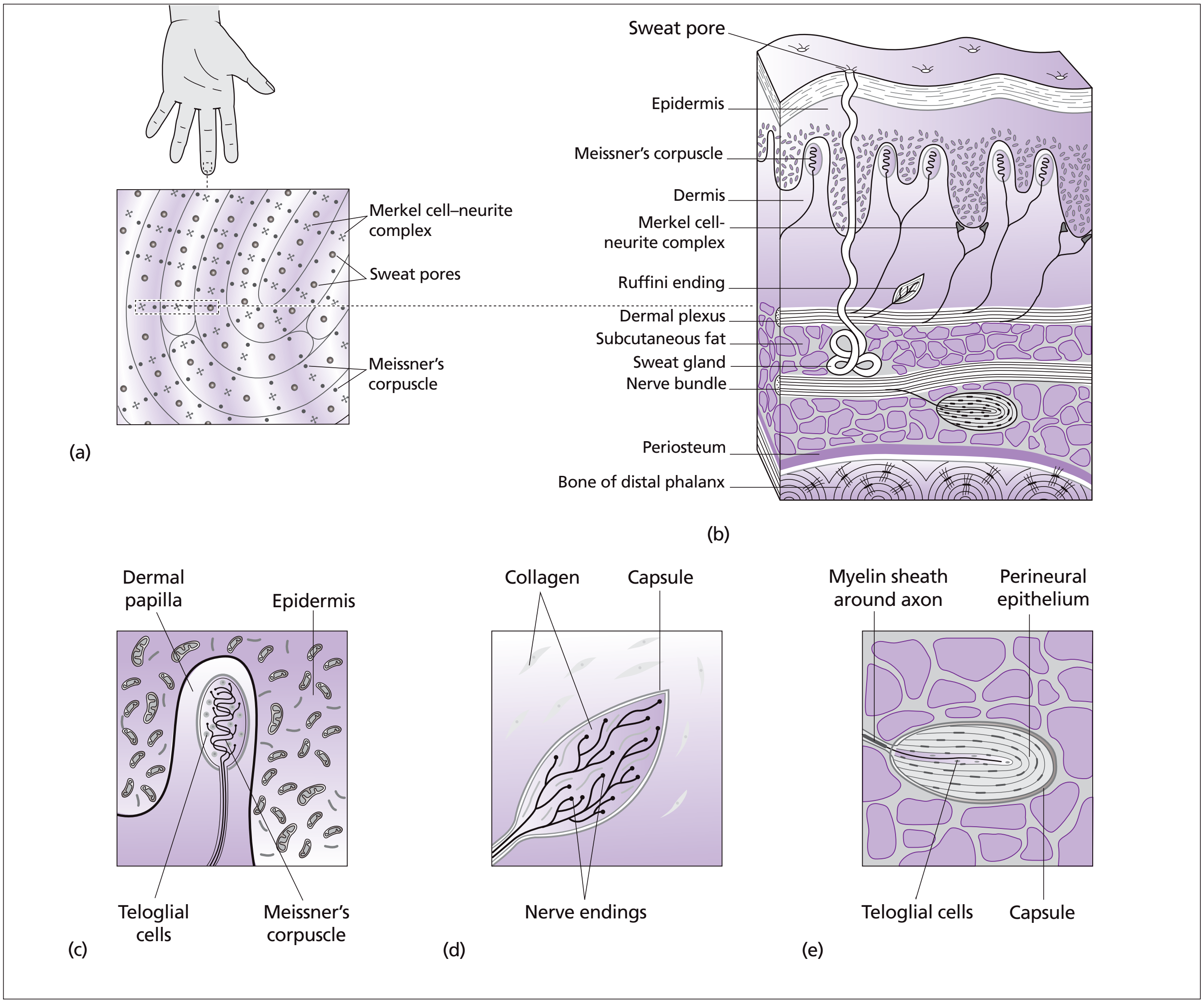

Merkel cell–neurite complex
Sweat pores
Meissner's corpuscle
(a)
Sweat pore
Epidermis
Meissner's corpuscle
Dermis
Merkel cell-neurite complex
Ruffini ending
Dermal plexus
Subcutaneous fat
Sweat gland
Nerve bundle
Periosteum
Bone of distal phalanx
(b)
Dermal papilla
Epidermis
Teloglial cells
Meissner's corpuscle
(c)
Collagen
Capsule
Nerve endings
(d)
Myelin sheath around axon
Perineural epithelium
Teloglial cells
Capsule
(e)

Figure 2.9 Example of nerve endings in non-hairy skin. (a) Finger tip: Meissner's corpuscles and Merkel cell–neurite complexes. (b) Section through skin of finger tip. (c) Meissner's corpuscle. (d) Ruffini ending. (e) Pacinian corpuscle.

Nerve endings are:

- Free;
- Follicular;
- Encapsulated; or
- Merkel–neurite complexes;
- Muscle spindle flower spray and annulospiral endings.

Free nerve endings (naked axons) that have lost both peri-neural and myelin sheaths form a dermal and subepidermal network and innervate joints, ligaments and capsules. Some are thermoreceptors, others nociceptors. Some nociceptors (from finely myelinated Aδ fibres) respond fast to severely painful stimuli (e.g. pinching). Others, from slowly conducting C fibres, are polymodal nociceptors, capable of sensing mechanical stimuli, heat, cold and chemical irritants. The axon reflex is mediated by C fibres.

Follicular nerve endings fire when a hair is being bent. A circumferential rim of nerve terminals surround an inner palisade, adjacent to each follicle.

Meissner's and Pacinian corpuscles and Ruffini endings are encapsulated by an inner membrane of modified Schwann cells (teloglia), a middle peri-neural layer and an outer coat of connective tissue. All are mechanoreceptors:

- Meissner's corpuscles, most numerous on finger pads, detect delicate changes in texture (to 20 μm in elevation) and are rapidly adapting.
- Pacinian corpuscles are subcutaneous, 2–3 mm in diameter and are plentiful (approximately 300) in each hand and foot and also embedded in the periosteum in the limbs. They are exquisitely sensitive to vibration, object detection and release.

- Ruffini endings in the skin respond to shearing stress (skin movement).

Merkel–neurite complexes are expanded nerve terminals applied to Merkel cells (tactile menisci) in the skin basal epithelium. They respond to sustained pressure. These mechanoreceptor afferents are separated into four types using the Johansson–Vallbo classification. The pathophysiology of individual types of nerve terminal is in its infancy, but presumably changes within these sensitive structures cause unpleasant sensory symptoms.

Muscle spindle motor supply, annulospiral and flower spray endings

Primary Type Ia sensory fibres with annulospiral endings surround each intrafusal muscle fibre. Secondary Type II fibres (flower spray endings) lie beside each annulospiral ending. Fusimotor fibres are Aγ calibre and innervate the contractile intrafusal fibres of the muscle spindle, in contrast to the Aα extrafusal fibres of skeletal muscle (Figure 2.10).

Golgi tendon organs

Type Ib afferents form an entwining network around tendons. Golgi tendon organs signal force of contraction and effect negative feedback on agonist–antagonist muscle groups. An important function is to restrict joint oscillation.

THE WORKING BRAIN

Introduction

Neurones and glia are the structural and functional units of all parts of the nervous system. The remainder of this chapter outlines how these different parts operate, their structure and the connections between them. Some basic understanding of neuroanatomy is assumed, and is readily available from reference texts.

The approach here is to take a typical activity, to trace its origins, describe its features and outline neuro-anatomical pathways and control systems. Movement is discussed first, because it has a pivotal role in clinical assessment.

Mechanisms of movement

Skilled, coordinated, fast and appropriate movement is so highly developed in humans that almost all parts of the nervous system are involved – alertness, cognition, volition, mood, all sensory stimuli – vision, hearing, touch, pain, position sense, smell and the motor cortex, with the associated cortical areas, the spinal reflex arc, cerebellum, basal ganglia, motor nerves, neuromuscular junction and muscles themselves. The essential objects of

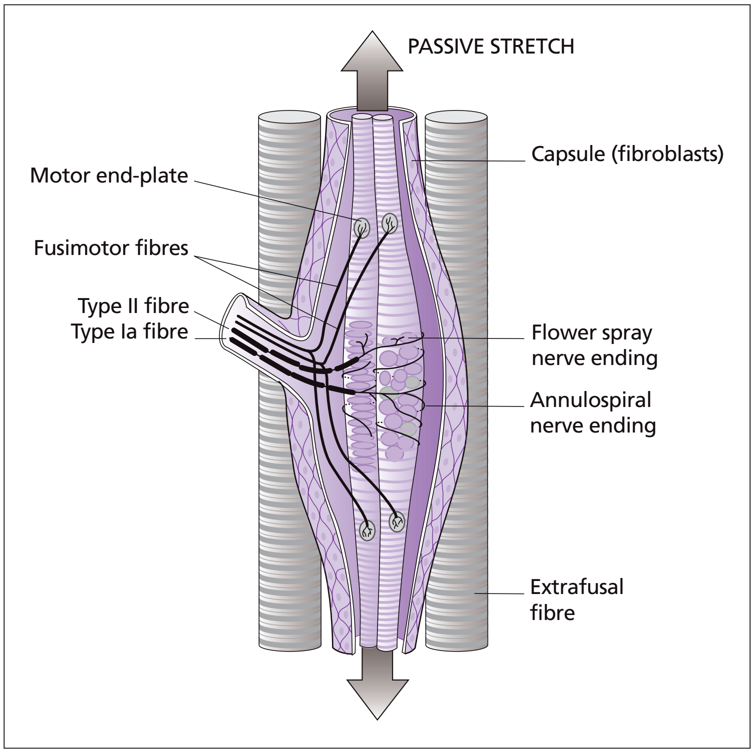


Figure 2.10 The muscle spindle.

movement are feeding, survival and, where possible, reproduction. In humans, movement assumed signal importance in the development and progressive use of tools to an extent that far exceeds the capacity of any non-human species.

Three central systems of motor control

All human movement is the product of activity in a highly interconnected motor network. All of the major motor pathways that generate eye, head, body and limb movements are under the control of three major systems:

- Cortical;
- Striatal (basal ganglia); and
- Cerebellar.

The major output from this network controlling limb movements is the corticospinal tract. This pathway originates from motor, somatosensory and limbic areas of the cortex; because all its fibres pass through the medullary pyramids at brainstem level, it is often referred to as the pyramidal tract. The tract is particularly well-developed in humans. Clinically, interruption of these fibres is recognized by abnormal signs of voluntary movement – weakness and poverty of movement, and abnormal reflex activity. The clinical signs associated with damage to the basal ganglia and cerebellum are fundamentally different.

The three systems referred to above are involved in two major motor loops: the cortex–basal ganglia–cortex loop and the cortex–cerebellum–cortex loop. The cortico-striatal and cortico-pontine fibres that provide the respective cortical projections into these two loops are very extensive. For the neurologist, the distinctive signs of damage to the basal ganglia are usually referred to as ‘extrapyramidal’ to distinguish them from the clinical signs of ‘pyramidal’ damage. However, while both the cerebellum and the basal ganglia influence eye and head movement mainly through their outputs to brainstem structures, it is the cortico-spinal system that provides the major output conduit for the activity generated in these two major motor loops that lead to limb movements. Therefore, it is important to distinguish ‘extrapyramidal’ signs or syndromes, a universally useful clinical term, but to be wary of the term ‘extrapyramidal pathways’. This is because the latter implies activity in non-corticospinal pathways, i.e. those involving the basal ganglia. This cannot be reconciled with the fact that the main basal ganglia output pathway influencing movement is via its return projections via thalamus to cortex, and thence through the corticospinal ‘pyramidal’, tract.

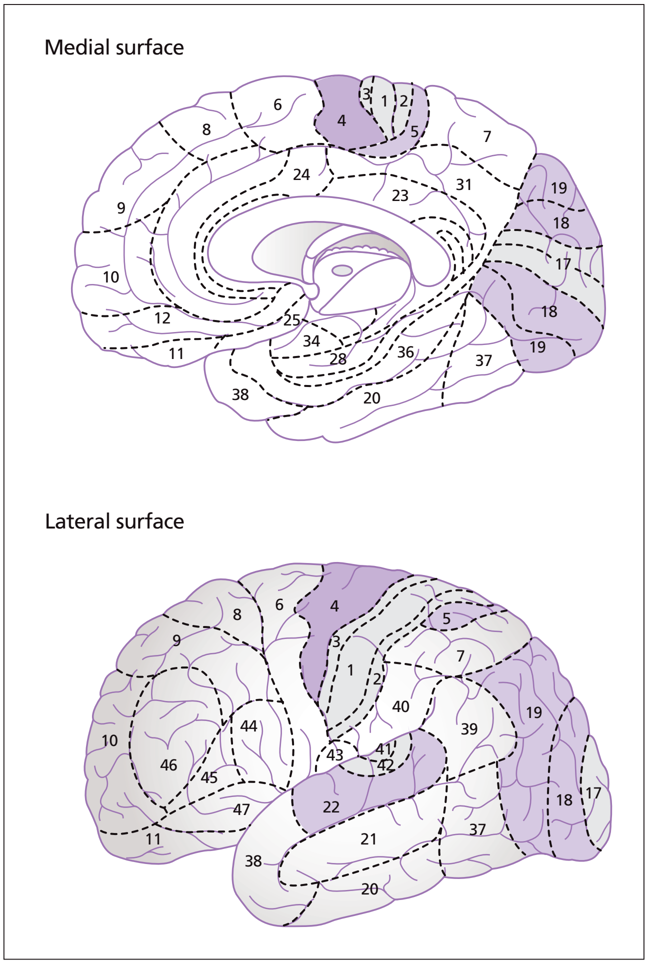
The corticospinal (pyramidal) system originates in the cortex and delivers information to all regions of the spinal cord including anterior horn cells, (spinal motor neurones). Defective function is recognized from the distinct abnormal pattern of skilled voluntary movement, spasticity and reflex change.

The striatal (basal ganglia) system facilitates fast fluid movement via servo loops between cortex and basal ganglia. To the clinician, slowness (bradykinesia), stiffness (rigidity), rest tremor and various disorders of movement (dyskinesias) are the hallmarks of dysfunction in this system, often referred to as ‘extrapyramidal’ signs or syndromes.

The cerebellum and its connections have a role in the coordination of smooth, programmed movement and balance. Ataxia (limb and/or truncal) and action tremor are the cardinal features.

Corticospinal (pyramidal) system

Penfield’s human cortical electrical stimulation experiments in the 1930s explored and mapped areas 4 (primary motor cortex,


Medial surface

Lateral surface

Figure 2.11 Cortical areas. (After Brodmann 1906.)

Principal motor areas	
4	Primary motor cortex, M1
6	Supplementary motor area (medial surface), SMA
6	Premotor area (lateral surface), PMA
23, 24	Cingulate motor areas
Principal sensory areas	
3, 2 and 1	Primary somatic sensory cortex, (SI)
40	Secondary somatic sensory cortex, (SII)
17	Primary visual cortex
18,19	Visual association cortex
41,42	Primary auditory cortex (buried from view, on superior temporal gyrus)
22	Auditory association cortex

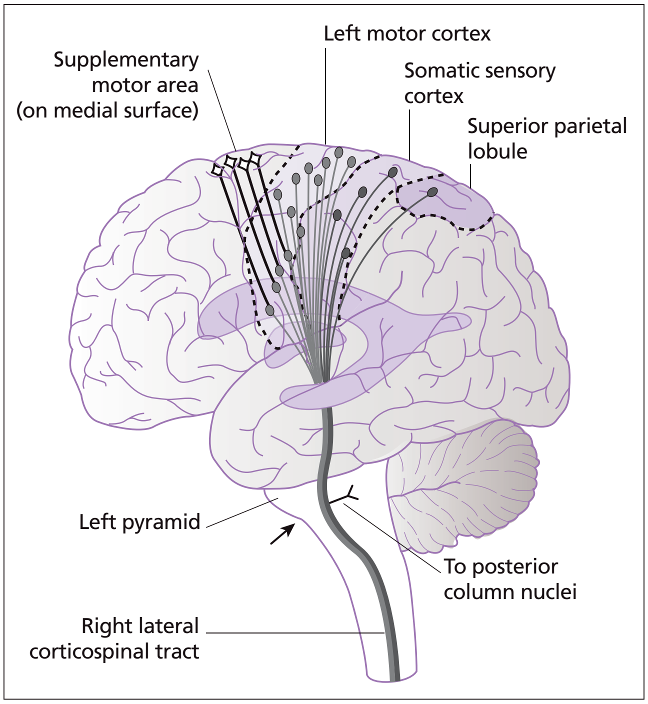

Left motor cortex
Supplementary motor area (on medial surface)
Somatic sensory cortex
Superior parietal lobule
Left pyramid
To posterior column nuclei
Right lateral corticospinal tract

Figure 2.12 Cortical contributions to pyramidal tract.

M1) and 6 (premotor area + supplementary motor area; PMA + SMA), developing the earlier work of Fritsch and Hitzig in the 1870s and individual observations by Ferrier, Sherrington, Campbell and others in the late 19th and early 20th century. Brodmann's cortical areas are shown in Figure 2.11 and the cortical contribution to the corticospinal pathway in Figure 2.12, noting the contributions from primary somatosensory cortical areas 1, 2 and 3 – and all cortical sensory areas concerned with movement towards or away from an object. It is likely that a significant corticospinal projection also arises from the cingulate gyrus (areas 23 and 24).

Each corticospinal tract is made up of around 1.1×10^6 fibres and is one of the longer and most compact fibre systems in the human CNS. Some two-thirds of these axons originate from cortical areas 4 and 6, where the cell bodies are located in lamina V. Most of the remainder derive from parietal areas, including the somato-sensory cortex, posterior parietal cortex and area SII. The course of 90% of the fibres through the internal capsule, cerebral peduncle, pons and medulla is shown in Figure 2.13.

Pyramidal describes the roughly triangular cross-section of this tract in the medulla (see below), but has come to be used functionally (and interchangeably) with corticospinal to describe the pattern of physical signs with disease of this pathway. In fact, probably around 75% of the pyramid fibres continue into the spinal cord. After decussation, the fibres congregate within the cord in the lateral corticospinal tract and terminate widely along the whole length of the spinal cord, and in all layers of the spinal grey matter, including synapses on motor neurones in the anterior horn. Of corticospinal fibres, 10% remain uncrossed, their neurones of origin outlining an ipsilateral somatotopic map, a point of little apparent clinical significance.

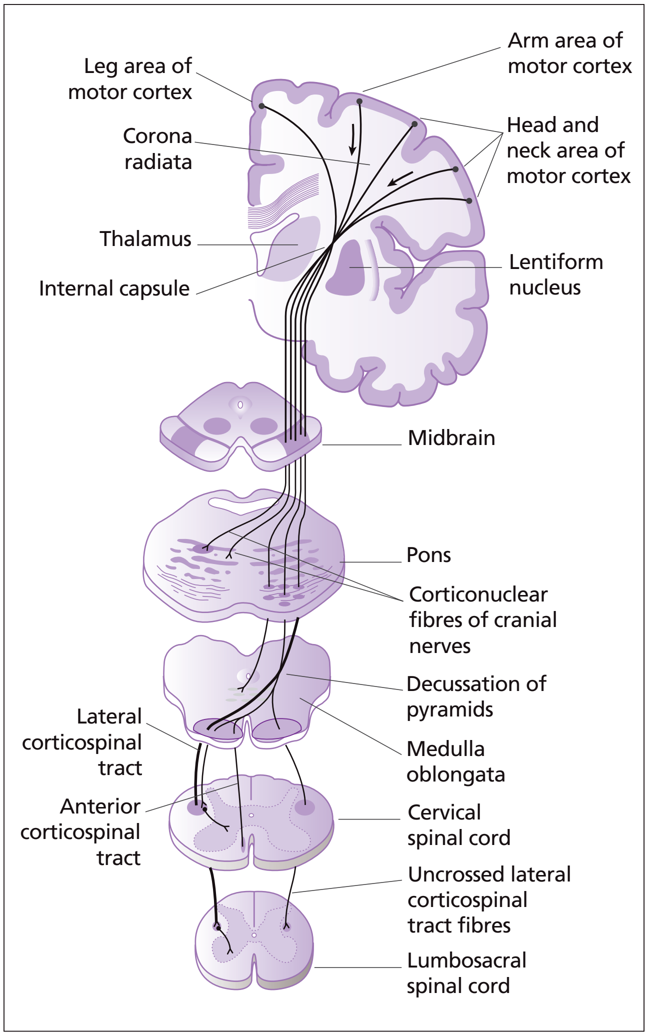

Leg area of motor cortex
Arm area of motor cortex
Corona radiata
Head and neck area of motor cortex
Thalamus
Internal capsule
Lentiform nucleus
Midbrain
Pons
Corticonuclear fibres of cranial nerves
Decussation of pyramids
Lateral corticospinal tract
Medulla oblongata
Anterior corticospinal tract
Cervical spinal cord
Uncrossed lateral corticospinal tract fibres
Lumbosacral spinal cord

Figure 2.13 Corticospinal (pyramidal) motor pathways.

The comparative anatomy of the motor pathways shows us that in humans the corticospinal system is the major descending pathway and has to some extent replaced other descending systems. For example, the rubrospinal tract, which arises from the magnocellular divisions of the red nucleus, is probably vestigial in humans.

Movement direction and movement synergy

Neurones in area 4 are known to show patterns of activity that implicate them in the control of key parameters of movement, such as force, direction and timing of movements. The motor areas probably function to activate particular synergies of muscular action to bring about highly specific movements such as particular types of grasp. These synergies depend in part on the pattern of innervation by the direct cortico-motoneuronal projections from primary motor cortex to specific groups of motor nuclei at spinal level.

Plasticity

In all primates, small cortical lesions cause initial paralysis (or slowing, depending on lesion size) of a limb, or part of a limb, followed by recovery within hours or days. This recovery is explained by changes in neighbouring cortical cell columns, i.e. plasticity. In the cord, local interneuronal mechanisms underpin movement synergies that function to provide individual skilled movements under the influence of different cortical signals. At a clinical level, following a hemiparesis, the early return of some fine finger or toe movement is a pointer to good recovery of function – a signal that a plastic process of compensation for the damage is under way.

Afferents to the primary motor cortex

The primary motor cortex does not act in isolation as the generator of fast skilled movement. Substantial afferent connections arrive from:

1 The opposite cortex via the corpus callosum. Most prominent are the dense links between cell columns controlling axial mucles, while the least dense are between distal parts of the opposite limbs. This might be expected – head and trunk posture cannot be under unilateral control, whereas the opposite is the case for fine hand movement.

2 Somato-sensory cortex. Cutaneous cell columns (areas 1, 2 and 3b) pass forward via short association fibres deep to the central sulcus. Typically, the more complex the subserved movement function (e.g. hand movements), the denser the connections. Proprioceptive cell columns in area 3a receive afferents from muscle spindles and synapse via short association fibres with area 4.

3 Cerebellum, via contralateral dentate nucleus and motor thalamus. Cerebellar impulses determine synergy and timing of cortical neuronal discharges (see below). The cerebellum receives a dense multimodal input of all sensory modalities, including vision.

4 Supplementary motor area (SMA, area 6) on medial surface of hemisphere. This part of area 6 is especially involved in motor planning, motor memory, intention and responds to internal cues. For example, the SMA is activated via the frontal lobe when a movement is intended. A major SMA function is programming motor sequences already within motor memory via a loop through the basal ganglia and projecting to area 4. Unilateral damage to SMA causes contralateral akinesia.

5 Premotor cortex (PMC, area 6 on lateral aspect of hemisphere). The PMC, some six times the size of area 4, is in general responsive to external cues, being active (on functional magnetic resonance imaging [fMRI]) when motor sequences follow visual or sensory cues, e.g. reaching for an object in view or feeling the shape of an object. The lateral PMC represents one of the major pathways through which vision is able to control fine movements.

Basal ganglia and 'extrapyramidal' movement disorders

The term basal ganglia describes neighbouring areas within the deep forebrain and midbrain involved in the control of movement. In practical terms this includes:

- The striatum (caudate nucleus, putamen of lentiform nucleus, nucleus accumbens);
- The pallidum (globus pallidus of lentiform nucleus) – a lateral and medial segment. The medial segment has as an anatomical extension, the pars reticularis of the substantia nigra;
- The subthalamic nucleus; and
- The pars compacta of the substantia nigra.

The complex circuitry between these anatomically recognizable structures is outlined here. The subject is not made easy by two factors: the difficulty distinguishing clear differences in ultrastructure between different parts of the basal ganglia – striatal neurones appear randomly scattered – and difficulty recognizing somatotopic differentiation in the majority of these structures, although such organization into body maps in the basal ganglia certainly exists. In many instances (cf. the cerebral cortex) individual diseases do not appear to affect one discrete area within this region, and thus localization of function to a particular zone is not immediately recognizable. These factors led in part to a paucity of interest in very evident disorders of movement in classical early 20th century neurology. Functional stereotactic surgery, deep brain stimulation, fMRI and advances in knowledge of the functions of neurotransmitters within the basal ganglia have brought a different focus to this field.

Extrapyramidal, the term coined by Kinnier Wilson in the 1920s, implies a loose but valuable recognition of clinical features of disorders of these structures. The term really implies no more than a clinical pointer towards a movement disorder distinct from one with hallmarks of corticospinal (pyramidal) or cerebellar disease. As noted above, care should be used to distinguish the clinically useful term 'extrapyramidal syndrome' from its use to describe a 'system' or 'pathway'. Usually, 'extrapyramidal syndrome' describes slowing and stiffness seen typically in idiopathic Parkinson's disease and more generally in the parkinsonism of other akinetic-rigid syndromes. However, extrapyramidal is also used (less frequently) to include many disorders of movement: tremor, chorea, hemiballismus or dystonia.

Basic circuits within the basal ganglia

The clinical focus is upon the complex motor loops, with dysfunction typified by Parkinson's disease.

Motor loops

There are a number of different neuronal servo-loops commencing and ending in the motor and frontal areas of the cerebral cortex. They all involve cortical projections to the striatum (putamen + caudate nucleus) and return projections to the cortex via different subnucleal divisions of the thalamus.

Within each loop there exist two interrelated motor pathways: direct and indirect pathways.

Transmission through the loops is controlled by activity in the nigro-striatal pathway, from the pars compacta of the substantia nigra to the lateral globus pallidus, where axons make two principal types of synapse, on excitatory D_1 (dopaminergic, direct pathway) and inhibitory D_2 (indirect pathway) receptors. Matters have become more complex with the discovery of several more dopaminergic receptor D subtypes.

In normal subjects, the nigro-striatal tract is tonically active, selecting preferentially the excitatory, direct pathway and leading, via the loop back to the cortex, to activation of the SMA before a movement. This early activation of midline cortex is thought to underlie the electrical readiness potential (Bereitschaftspotential). Other projections to the motor cortex interact with those from the cerebellum in modulating motor cortex outputs to the spinal cord.

Activation of the cortex (i.e. the intention to move):

- Stimulates (glutaminergic) putamen neurones (tonically facilitated by niagro-striatal D_1 input); which
- Inhibit (GABAergic) medial globus pallidus neurones; which
- Release (disinhibit) ventral lateral nucleus (VL) neurones; which
- Activate SMA.

The sequences can be seen in Figure 2.14.

The indirect pathway engages the subthalamic nucleus via:

- Striato-nigral fibres that inhibit putamen neurones; which
- Inhibit the lateral globus pallidus (GPL); and
- Act on the subthalamic nucleus (STN).

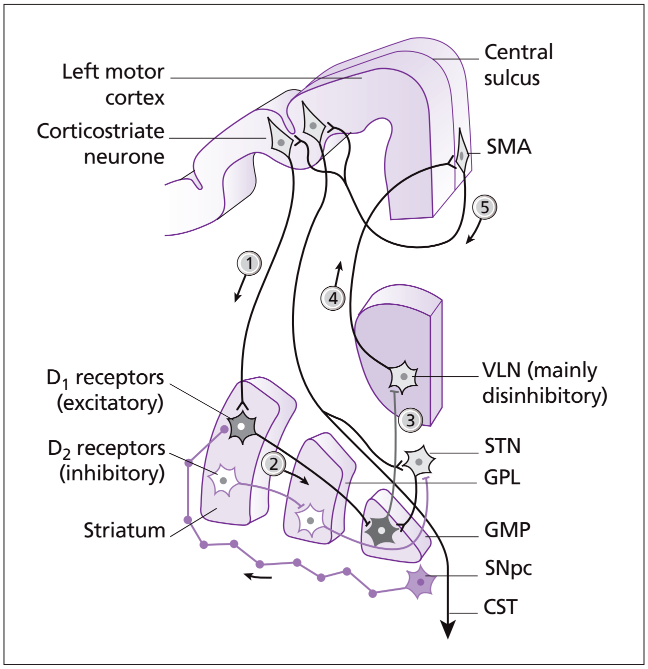


Figure 2.14 Striatal motor loops. CST, cortico-spinal tract; GPL, globus pallidus (lateral); GPM, globus pallidum (medial); SMA, supplementary motor area; SNpc, substantia nigra pars compacta; VLN, ventro-lateral nucleus (thalamus).

The subthalamic nucleus acts on the medial pallidum (somatotopically) to suppress unwanted movement. Destruction of the STN results in uncontrollable movements (see Hemiballismus, Chapter 5).

Normal functions of the motor loop

The basal ganglia do not initiate movement but they are active when action is generated by specific cell assemblies in the motor cortex:

- Scaling strength of muscle contraction and in collaboration with SMA;
- Programming appropriate movement sequences and suppressing others; and
- Controlling speed of movement

The putamen is believed to act as a store of memorized, acquired motor programmes, with an ability to sequence appropriately movements intended and pass information to the SMA.

Other basal ganglia circuits

- Cognitive loop: motor (volitional) intention;
- Limbic loop: emotional correlates of movement;
- Oculomotor loop: voluntary saccadic movements.

Cognitive loop

A large projection of fibres from the prefrontal cortex reaches the head of the caudate nucleus. Increased activity in the head of the caudate, and anterior putamen, globus pallidus and ventral anterior (VA) thalamic nucleus, occurs when new movements are performed by the opposite hand, suggesting a role in motor learning. The VA nucleus projects to:

- The premotor cortex in an 'open cognitive loop';
- The prefrontal cortex in a 'closed cognitive loop'.

These cortical connexions of the caudate point to a role of this loop in forward planning of complex motor intentions. As a corollary, when a motor task has become automatic, i.e. entirely learnt, the motor loop of the basal ganglia takes over.

Patients with Parkinson's disease have particular problems with new fiddly movements; they are unable to sequence and initiate them. Exceptional activity in this cognitive loop perhaps explains also rare temporary release phenomena: immobile patients with severe Parkinson's respond dramatically to great emotional stimulation – 'they can run down the fire escape'.

Limbic loop

This describes a loop from:

- Inferior prefrontal cortex; via
- Nucleus accumbens;
- Ventral pallidum;
- Medio-dorsal nucleus of thalamus; to
- Inferior frontal cortex.

This pathway is believed to be concerned with the visible expression of emotion – portrayed in facial expression (e.g. smiling), or in more general postures with emotional content such as submission, dominance or aggression.

The simian posture and facial masking of Parkinson's disease can be explained by diminution of activity in this richly dopaminergic pathway – features reversed, at least in part, by levodopa.

Oculomotor loop

This loop runs from:

- Frontal eye field and posterior parietal cortex (area 7); to
- Caudate nucleus; to
- Pars reticularis of substantia nigra (SNpr); to
- VA nucleus of thalamus; to
- Frontal eye field and prefrontal cortex.

An inhibitory GABAergic projection reaches the superior colliculus from SNpr. These inhibitory synapses are on neurones controlling saccades. Ocular fixation is accompanied by repetitive impulses (tonic activity) in SNpr. In other words, the eyes are held in one position of fixation by this tonic activity.

When a deliberate saccade takes place ('I want to look right'), the superior colliculus is disinhibited by the activated oculomotor loop. The superior colliculus neurones discharge, reinforcing the direct motor loop and facilitating rapid (almost instantaneous, 70–100 km/hour) conjugate eye movement. Put another way, the sequence is:

- Release of superior colliculus neurones;
- Gaze flicks to new target;
- SNpr resumes tonic activity;
- Gaze vigilance returns.

Slow eye movement (oculomotor hypokinesia) is evident in Parkinson's disease, although it is rarely a clinical issue because the accompanying axial movement (e.g. head turning) is slow. Ocular hypokinesia is explained by loss of dopamine in SNpr, and faulty disinhibition of superior colliculus neurones.

Cerebellum

To the clinician, cerebellar disease is recognized by the physical signs of action tremor, nystagmus, truncal and/or gait ataxia and scanning speech (Chapter 16).

Phylogenetically, functions of the cerebellum in fish were closely allied to the lateral line organs (fish vestibular system) – controlling the fish's horizontal and vertical posture in water. In quadrupeds, connections with the spinal cord became prominent, facilitating improvement in gait, running and turning. In bipeds, with emerging lateralized skills (e.g. hand) rich linkages developed between cerebellar lobes and cerebral cortex. These newer cerebellar structures became intimately concerned with coordination of ipsilateral limbs in addition to the vestibular and spinal phylogenetic heritage of this part of the hind brain. These aspects are illustrated in Figure 2.15.

There are three main zones of the cerebellum, each of which send its output to a distinct deep cerebellar nucleus:

1 Vestibulo-cerebellum is the central strip (vermis + fastigial nucleus), with primarily sensory afferents from the vestibular complex. Output: fastigial nucleus and brainstem vestibular nuclei.

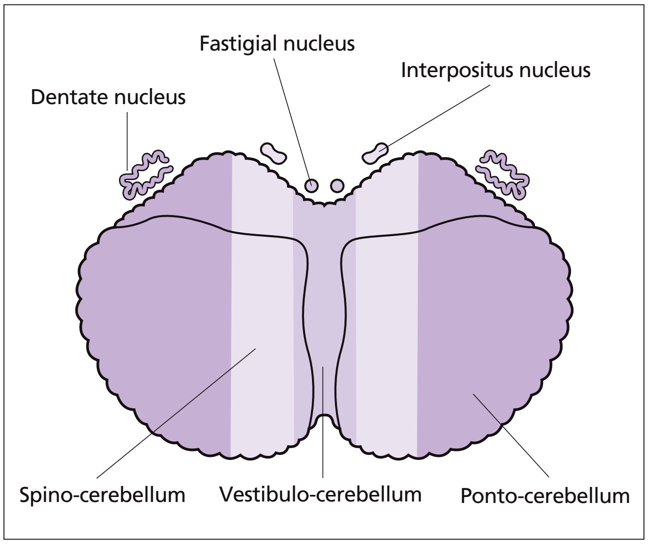


Figure 2.15 Zones of the cerebellum.

2 Spino-cerebellum occupies regions adjacent to the vermis, with major sensory input from the spinal cord. Output: interpositus nucleus.

3 Ponto-cerebellum (neo-cerebellum – lateral lobes) receives a massive neuronal input from the contralateral pontine nuclei, the main input of which comes from the cerebral cortex. Output: dentate nucleus. The neo-cerebellum is most developed and largest in humans.

Cellular anatomy

The cerebellar cortex has an outer molecular layer, an inner granular layer, with the piriform layer between the two (Figure 2.16). The granular layer consists of billions of small 6–8 μm diameter neurones (granule cells) with short dendrites. These dendrites receive excitatory synapses from mossy fibres that run to the cerebellar cortex, giving off collateral branches to the deep cerebellar nuclei. Granule cell axons pass to the outer molecular layer, dividing to form parallel fibres, running parallel to the cerebellar folia, to make excitatory synaptic contacts with dendrites of Purkinje cells whose cell bodies lie in the piriform layer.

Purkinje cells, large neurones with extensive dendritic trees, are interwoven by numerous parallel fibres. Each parallel fibre makes successive single (one-per-cell) synapses with 300–500 individual Purkinje cells. The action of each parallel fibre is excitatory – although many thousand parallel fibres need to act simultaneously to depolarize a single Purkinje cell.

From the contralateral inferior olivary nucleus, each Purkinje cell dendritic tree receives a single climbing fibre. This fibre makes synaptic contact with thousands of dendritic spines of a single Purkinje cell. A single action potential in a climbing fibre triggers a short burst of action potentials from each Purkinje cell, which then becomes temporarily unresponsive to the effects of parallel fibre inputs. Purkinje cell axons leave the cerebellar cortex, the only efferent axons to do so, to reach the deep

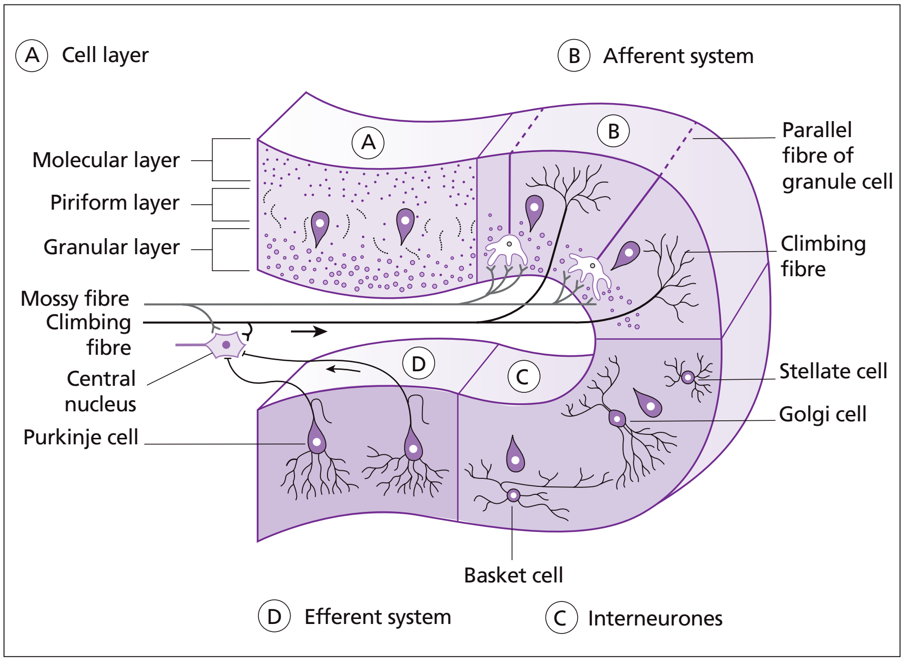

Ⓐ Cell layer
Ⓑ Afferent system
Molecular layer
Piriform layer
Granular layer
Mossy fibre
Climbing fibre
Central nucleus
Purkinje cell
A
B
C
D
Parallel fibre of granule cell
Climbing fibre
Stellate cell
Golgi cell
Basket cell
Ⓓ Efferent system
Ⓒ Interneurones

Figure 2.16 Cerebellar cortex cell systems.

cerebellar nuclei, upon which they exert a uniformly inhibitory action.

The molecular layer contains three further, largely inhibitory cell types: basket cells, stellate cells and Golgi cells.

Somatotopic representation in the cerebellum

Positron emission tomography (PET) and fMRI have largely confirmed the somatotopic representation deduced from animal studies (Figure 2.17). Corresponding fMRI activity for hand movement in humans is shown in Plate 2.2.

Afferent cerebellar pathways

The scope and complexity of these pathways is summarized here:

- From muscles and skin (trunk and limbs), information from the posterior spino-cerebellar and cuneo-cerebellar (cuneiform nucleus) tracts enter via each ipsilateral inferior cerebellar peduncle. The massive similar trigeminal input (from the head) enters via all three peduncles.
- Afferents monitoring activity in spinal reflex circuits, in the anterior spino-cerebellar tracts loop into each superior peduncle via the pons.
- Vestibular, auditory and visual pathways make up the tecto-cerebellar tracts to enter the ipsilateral superior peduncle.
- The ponto-cerebellar tract, mediating massive mossy fibre input from the cerebral cortex, enters the contralateral middle cerebellar peduncle.
- The olivo-cerebellar tract enters the contralateral inferior peduncle (climbing fibre input).

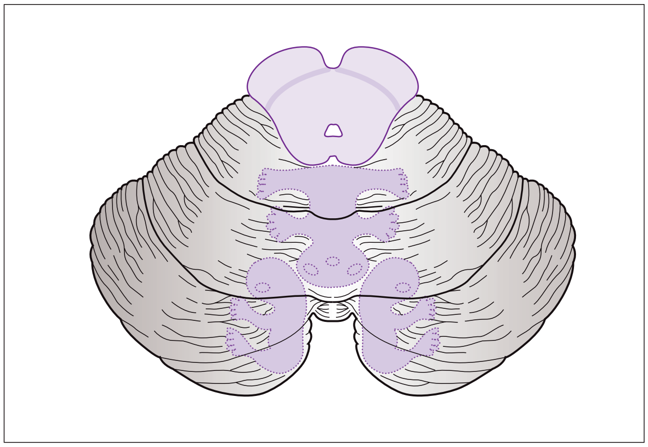


Figure 2.17 Somatotopic cerebellar mapping (based on animal data).

- Reticulo-cerebellar tracts enter via the inferior peduncles.
- Aminergic fibres (serotonin and noradrenaline) enter all three cerebellar peduncles from the brainstem – excitatory transmission in mossy fibres and climbing fibre terminals.

Olivo-cerebellar tract, learning, the red nucleus and novelty detection

The inferior and accessory olivary nuclei receive fibres from the ipsilateral sensorimotor (cerebral) cortex. These project as climbing fibres to each contralateral cerebellar cortex in a somatotopic order (accessory nuclei to an anterior cerebellar map, principal nuclei to posterior). When primates are trained to carry out a repetitive motor activity, Purkinje cells show increased simple spike activity – an indication of increased mossy fibre and parallel fibre input. If the task is interrupted (e.g. if activity is physically obstructed), bursts of Purkinje cell complex spikes appear, caused by climbing fibre input. At least, they do so initially. If the obstruction is sustained, these complex spike bursts diminish and eventually disappear. This is one example of the role of the cerebellum in learned movement, for which there is now much evidence both in animals and in humans. The system acquires, or adapts to new motor activity. Additional connections to the olivary nuclei come from the visual association cortex and the spino-olivary tract.

Finally, the red nucleus receives collaterals from (cerebral) cortical fibres descending to the olive, and from cerebellar efferents en route to the thalamus. The principal output from the red nucleus is inhibitory to the ipsilateral olive. There is evidence to suggest that if an imbalance occurs between movement intended (cerebral cortex) and movement organized/learned (cerebellum), the red nucleus modulates cell groups within the olive to achieve harmony, and it detects novelty in an organized action. The coarse tremor seen in lesions of the red nucleus can be thought of as a breakdown of this harmonic, over-correcting each part of a movement.

Efferent pathways

The vestibulo-cerebellum projects to the vestibular system, the spino-cerebellum to the cord and the neo-cerebellum to the red nucleus, thalamus and motor cortex.

From each fastigial nucleus in the vestibulo-cerebellum, via the inferior peduncles, axons reach both (right and left) vestibular nuclei (Figure 2.18). Output from the medial and superior vestibular nuclei passes to the medial longitudinal fasciculus, and thus control conjugate lateral gaze. From lateral vestibular nuclei (of Dieter), efferent fibres pass to the vestibulo-spinal tracts; these help control balance and axial stability. Some fastigial outputs pass directly to the spinal cord, for control of head and neck movements.

From each nucleus interpositus (spino-cerebellum) axons travel in the superior peduncle, ending largely in the contralateral reticular formation (posture, gait) and red nucleus (motor learning).

In the neo-cerebellum, outflow from the dentate nucleus makes up the majority of the superior peduncle (dentato-

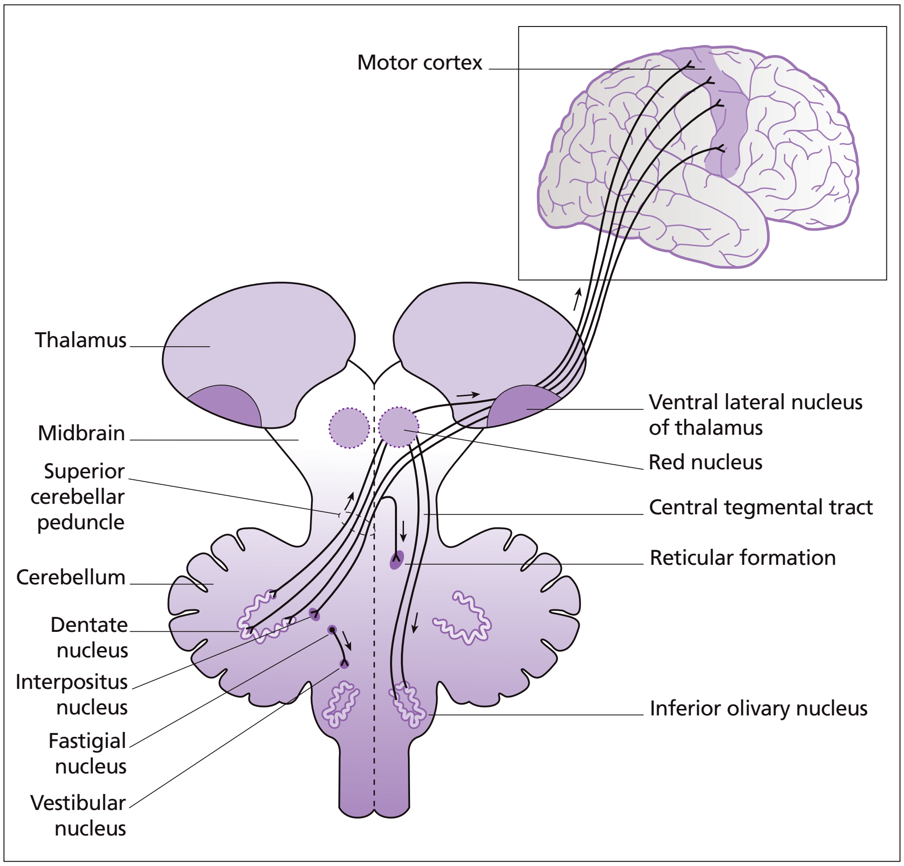

Motor cortex
Thalamus
Midbrain
Superior cerebellar peduncle
Cerebellum
Dentate nucleus
Interpositus nucleus
Fastigial nucleus
Vestibular nucleus
Ventral lateral nucleus of thalamus
Red nucleus
Central tegmental tract
Reticular formation
Inferior olivary nucleus

Figure 2.18 Cerebellar efferents.

rubro-thalamic tract), and crosses in the brainstem before reaching both red nucleus and motor thalamus. The latter sends onward projections to the cortex.

Clinical correlates

In contrast to the complexity of cerebellar micro-anatomy, physical signs of cerebellar disease are distinct, relatively straightforward to recognize but often hard to attribute to individual pathways (Chapters 3 and 16). A lesion of one lateral lobe, e.g. tumour or infarction, causes rebound and past pointing of the outstretched upper limb – a clinical correlate of the effect of obstruction to a programmed activity described above. Vermis lesions, e.g. medulloblastoma, affect primarily vestibular connexions. Truncal ataxia is often an early sign.

Anterior cerebellar lobe lesions (often bilateral, and typically caused by alcohol) cause gait ataxia, often with pronounced titubation. In chronic alcohol damage, substantial loss of all major neurone types develops (granular, Purkinje and molecular layer cells). Depression of tendon reflexes – an unusual cerebellar sign, and of rare clinical value – is explained by loss of tonic stimulation of fusimotor neurones connected via pontine reticulo-spinal fibres. Nystagmus (coarse, fast phase towards the side of the lesion, and dramatic when it occurs) is an inconstant feature of cerebellar lesions.

Finally, the (usually) temporary cognitive affective cerebellar syndrome is of interest. This comprises diminished reasoning, inattention, poor memory and flattening of affect, sometimes seen transiently after major cerebellar lesions, e.g following surgery or massive infarction. One explanation, suggested from functional imaging and some recent neuroanatomical studies, is temporary reduction in blood flow to cerebral cortical association areas, possibly because of diminution of expected impulses of cerebellar origin to the thalamus, and thence to prefrontal cortical areas.

Sensation and sensory pathways

The neurologist usually deals with sensation in its five clinical modalities: touch, nociception, temperature, joint position and vibration sense. The neuroscientist has a wider perspective, looking at sensation first as conscious or non-conscious. Conscious sensation is perceived, largely at cortical level. Non-conscious sensation is processed within the cortex too, but also within the cerebellum, via the vestibular system, in the reticular formation and widely within the CNS. It is often difficult to categorize clearly whether a sensation is conscious or non-conscious. For example, vertigo, the illusion of movement, is clearly conscious. However, the posture of the head in relation to the trunk is usually non-conscious. Both these sensations are mediated via vestibular pathways. Partly because of this problem, and in part because of the sheer complexity of the CNS, it is often hard to say where a particular sensory modality is localized or how it is perceived. Some of the essentials of the sensory pathways are summarized here, with a brief overview of a complex field. Circuitary within the spinal cord is dealt with in more detail in Chapter 15.

Conscious and non-conscious sensation

Conscious sensations are exteroceptive and proprioceptive. Exteroceptive sensations stimulate surface somatic receptors (e.g. touch, nociception, temperature) or telereceptors (vision, hearing, olfaction). Proprioceptive (conscious) sensations arise from joints, muscles, bones and the labyrinth. For example, vestibular pathways to the cortex enable us to perceive whether we are stationary or moving, and to discriminate between constant movement, deceleration and acceleration.

Non-conscious sensations are of two kinds:

- Afferent proprioceptive information (e.g. from muscles, joints, tendons, labyrinth) reaching the cerebellum, cortex, reticular formation and elsewhere; and
- Enteroception (e.g. afferents from the gut, heart or blood vessels).

Somatic sensory pathways in the cord and brain

Two major pathways deliver sensory information to the thalamus and thence to the cortex:

- Spinothalamic pathways (nociceptive);
- Posterior columns → medial lemnisci (touch, position, movement).

Each system consists of first, second and third order neurones. They have the following features in common:

- The cell bodies of first order neurones are in the posterior root (dorsal root) ganglia;
- Second order neurones decussate before reaching the thalamus;
- Third order neurones project from thalamus to cortex;
- There is somatotopic organization throughout the system; and
- Transmission can be controlled (inhibited/enhanced) between first to second, and second to third order neurones (see Gate control below, and Chapter 22).

Dorsal root ganglia – first order neurones

The arrangement of spinal nerves, dorsal and ventral roots, laminae of the posterior horn and named cell groups are illustrated in Figure 2.19. The complexity of information outlined in the figure is exemplified by the fact that a single nerve root ganglion serving a limb contains around 100,000 neurones, each enshrouded by satellite cells (modified Schwann cells).

Termination of dorsal root afferents

In the dorsal root entry zone, afferent fibres separate into medial and lateral streams. The lateral stream (Aδ and C fibres) divides into short ascending and descending branches within the posterolateral tract of Lissauer. They then synapse in lamina I (marginal zone), lamina II (substantia gelatinosa) and in III–V.

The medial stream (Type I and II mechano-receptors) divides into ascending and descending branches in the posterior columns.

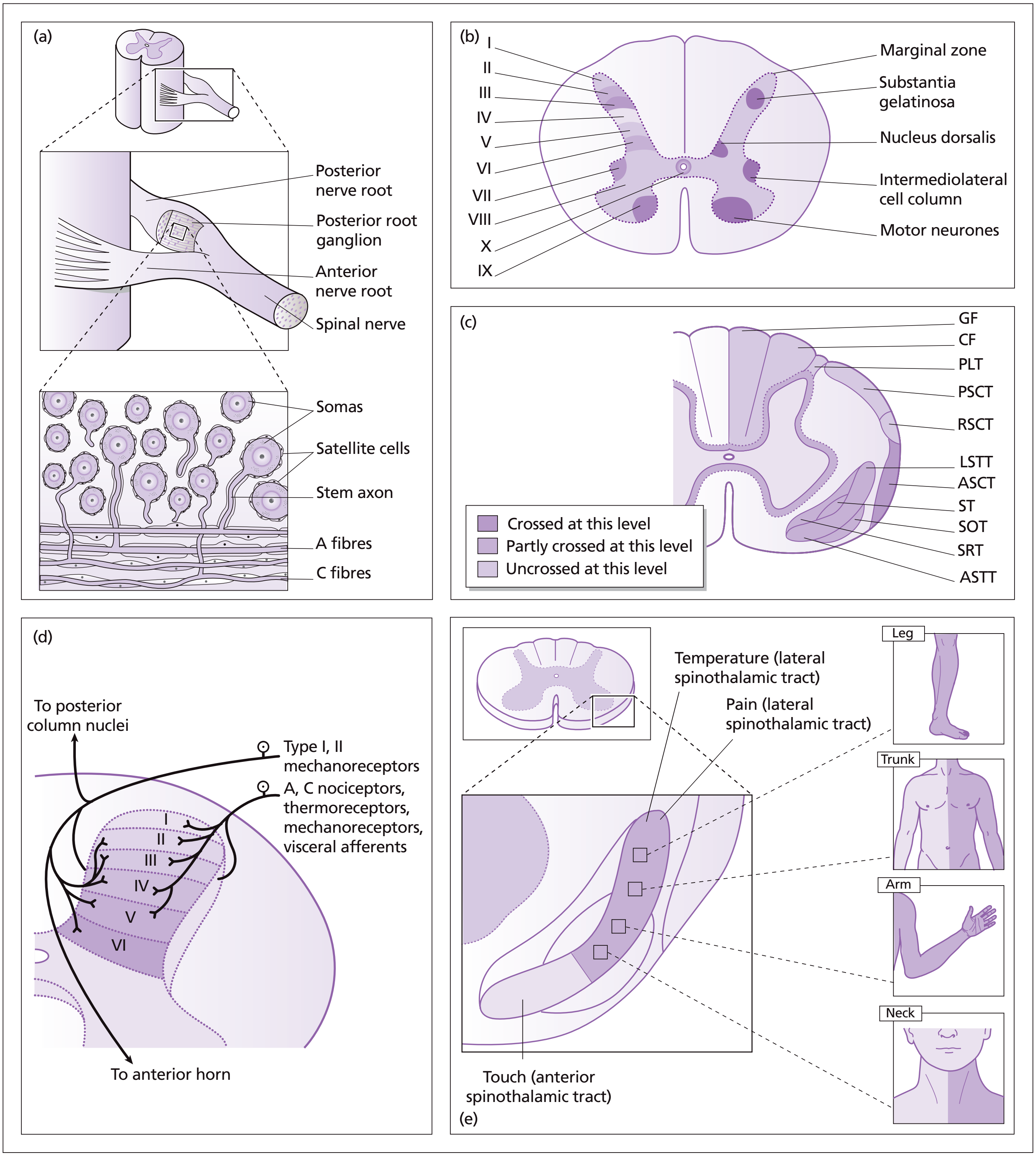

(a)
Posterior nerve root
Posterior root ganglion
Anterior nerve root
Spinal nerve
Somas
Satellite cells
Stem axon
A fibres
C fibres
(b)
I
II
III
IV
V
VI
VII
VIII
X
IX
Marginal zone
Substantia gelatinosa
Nucleus dorsalis
Intermediolateral cell column
Motor neurones
(c)
GF
CF
PLT
PSCT
RSCT
LSTT
ASCT
ST
SOT
SRT
ASTT
Crossed at this level
Partly crossed at this level
Uncrossed at this level
(d)
To posterior column nuclei
Type I, II mechanoreceptors
A, C nociceptors, thermoreceptors, mechanoreceptors, visceral afferents
I
II
III
IV
V
VI
To anterior horn
Temperature (lateral spinothalamic tract)
Pain (lateral spinothalamic tract)
Leg
Trunk
Arm
Neck
Touch (anterior spinothalamic tract)
(e)

Figure 2.19 Sensation. (a) Posterior root ganglion. In lower figure, note T-shaped bifurcation of stem fibres. (b) Laminae (I–X) and named cell groups at mid thoracic level. (c) Ascending pathways at upper cervical level. ASCT, anterior spino-cerebellar tract; ASTT, anterior spinothalamic tract; CF, cuneate fasciculus; GF, gracile fasciculus; LSTT, lateral spinothalamic tract; PLT, posterolateral tract; PSCT, posterior spino-cerebellar tract; RSCT, rostral spino-cerebellar tract; SOT, spino-olivary tract; SRT; spino-reticular tract; ST, spino-tectal tract. (d) Targets of primary afferent neurones in the posterior grey horn. (e) Sensory modalities in spinothalamic pathway at upper cervical level.

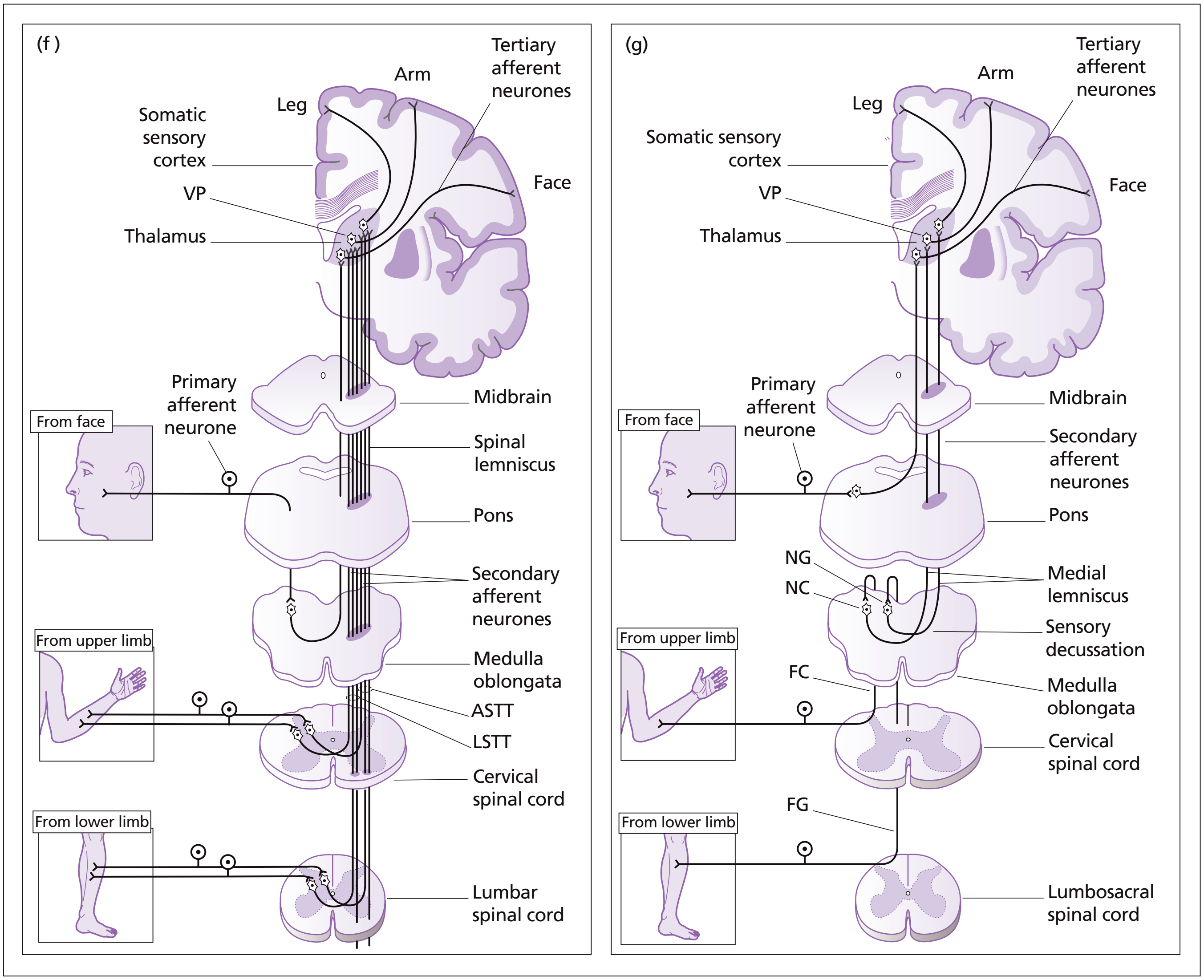

(f)
Tertiary
afferent
neurones
Arm
Leg
Somatic
sensory
cortex
Face
VP
Thalamus
Primary
afferent
neurone
From face
Midbrain
Spinal
lemniscus
Pons
Secondary
afferent
neurones
From upper limb
Medulla
oblongata
ASTT
LSTT
Cervical
spinal cord
From lower limb
Lumbar
spinal cord
(g)
Tertiary
afferent
neurones
Arm
Leg
Somatic sensory
cortex
Face
VP
Thalamus
Primary
afferent
neurone
From face
Midbrain
Secondary
afferent
neurones
Pons
NG
NC
Medial
lemniscus
Sensory
decussation
From upper limb
FC
Medulla
oblongata
Cervical
spinal cord
FG
From lower limb
Lumbosacral
spinal cord

Figure 2.19 *Continued* (f) The spinothalamic pathway. ASTT, anterior spinothalamic tract; LSTT, lateral spinothalamic tract; VP, ventral posterior nucleus of thalamus. (g) The posterior column → medial lemniscal pathway. FC, fasciculus cuneatus; FG, fasciculus gracilis; NC, nucleus cuneatus; NG, nucleus gracilis; VP, ventral posterior lateral and ventral posterior medial nuclei of thalamus.

The shorter branches synapse in laminae II, III, IV, V and VI. The longer branches run throughout the posterior columns of the cord to the gracile and cuneate nuclei in the medulla.

Posterior column → medial lemniscus pathway

The fascicles of the posterior columns of the cord are formed partly by axons of posterior root ganglia (first order neurones) and partly by axons of second order neurones in the dorsal horn of the spinal grey matter. These axons all project to the gracile and cuneate nuclei in the brainstem, whose axons then decussate in the medulla to form each medial lemniscus (ribbon) that terminates in the lateral part of the ventral posterior nucleus of the thalamus. Thalamo-cortical neurones (third, fourth order) then project to the somatic sensory cortex.

Spinothalamic pathway

The anterior and lateral spinothalamic tracts consist of second order neurones passing from laminae I, II, III, IV and V of the posterior grey horn to the opposite thalamus. The two tracts merge in the brainstem to form the spinal lemniscus and then enter the ventral posterior nucleus of the thalamus. Third order thalamic neurones project to the somatic sensory cortex.

Other ascending pathways

The two sensory pathways described above tend to dominate clinical neurology. Other important sensory pathways dealing more with non-conscious sensation are mentioned briefly here.

Spino-cerebellar pathways (four on each side) are concerned with non-conscious proprioception (P) and the interaction between spinal motor neurones and interneurones, i.e. the excitability of reflex arcs (R), and movements involving balanced activation of agonist and antagonist muscles:

- Posterior spino-cerebellar tract (P);
- Cuneo-cerebellar tract (P);
- Anterior spino-cerebellar tract (R);
- Rostral spino-cerebellar tract (R).

The spino-tectal tract passes information that relates to the orientation of the trunk and head towards a visual stimulus, from the spinal cord to the superior colliculus. This information is important in orientation reflexes to visual stimuli.

The spino-olivary tract sends tactile information to the inferior olivary nucleus and thence to the opposite cerebellar cortex. This pathway is believed to have an important role in motor learning.

Spino-reticular fibres originating in dorsal roots accompany the spinothalamic pathway in the cord. Their functions are arousal and reporting on the general content of a stimulus, e.g. whether it is noxious (pin-prick) or pleasurable (stroking). This is in contrast to the more analytical nature of the spinothalamic pathway which determines the precise nature, intensity and location of a stimulus.

The brainstem

One approach to the complexity of brainstem is to think of the region as a series of cell columns and fibre systems:

- Principal efferent (motor) pathways;
- Principal afferent (sensory) pathways;
- Cranial nerve nuclei;
- Reticular formation; and
- Traversing connections – autonomic, basal ganglia, cerebellar and vestibular.

As landmarks for localization, five simple guidelines are helpful:

1 Motor pathways lie in general ventrally.
2 Sensory pathways lie dorsally.
3 Cranial nerve nuclei (two longitudinal columns) denote the level in the superior–inferior (rostral–caudal) plane.
4 Most reticular formation (RF) nuclei lie laterally. Some (magnus raphe, median raphe) are midline.
5 Traversing connections (above) are found in all layers of the brainstem.

See also Chapter 3 (Figure 3.6).

Motor fibres

The cerebral peduncle transmits all the cortical efferent fibres to the brainstem (cortico-fugal fibres). Within the cerebral peduncle motor fibres are tightly packed. These are arranged, medially to laterally, to supply (Figure 2.20):

- Eye movements (E)
- Face (F)
- Upper limb (UL)
- Trunk (T)
- Lower limb (LL).

In the ventral pons motor fibres lie in separate bundles. Those for eye movements (E) and face (F) leave to reach their nuclei. The remaining bundles then recongregate in the upper medulla as the pyramidal tract or medullary pyramids. UL fibres remain medial; LL fibres lateral.

Crossing of motor fibres (pyramidal decussation) takes place below the medullary pyramids, so named because of the triangular cross-section of each. Topographical order is maintained: UL medial and LL lateral. UL fibres cross higher in the medulla than LL fibres. This makes it possible, although seldom seen, for tiny brainstem lesions to cause bilateral UL weakness (sparing LL), or weakness of one UL and the opposite LL, as well as the more common paraparesis with a brainstem lesion.

Motor fibres to cranial nerve nuclei

These cortico-bulbar motor fibres pass caudally in the genu (knee) of the internal capsule. Depending on the cranial nerve nucleus for which they are destined, some fibres cross the midline. They do so in varying proportions: some completely, some not at all and others in a ratio of about 50 : 50. Understanding these long-known innervation arrangements explains common clinical phenomena.

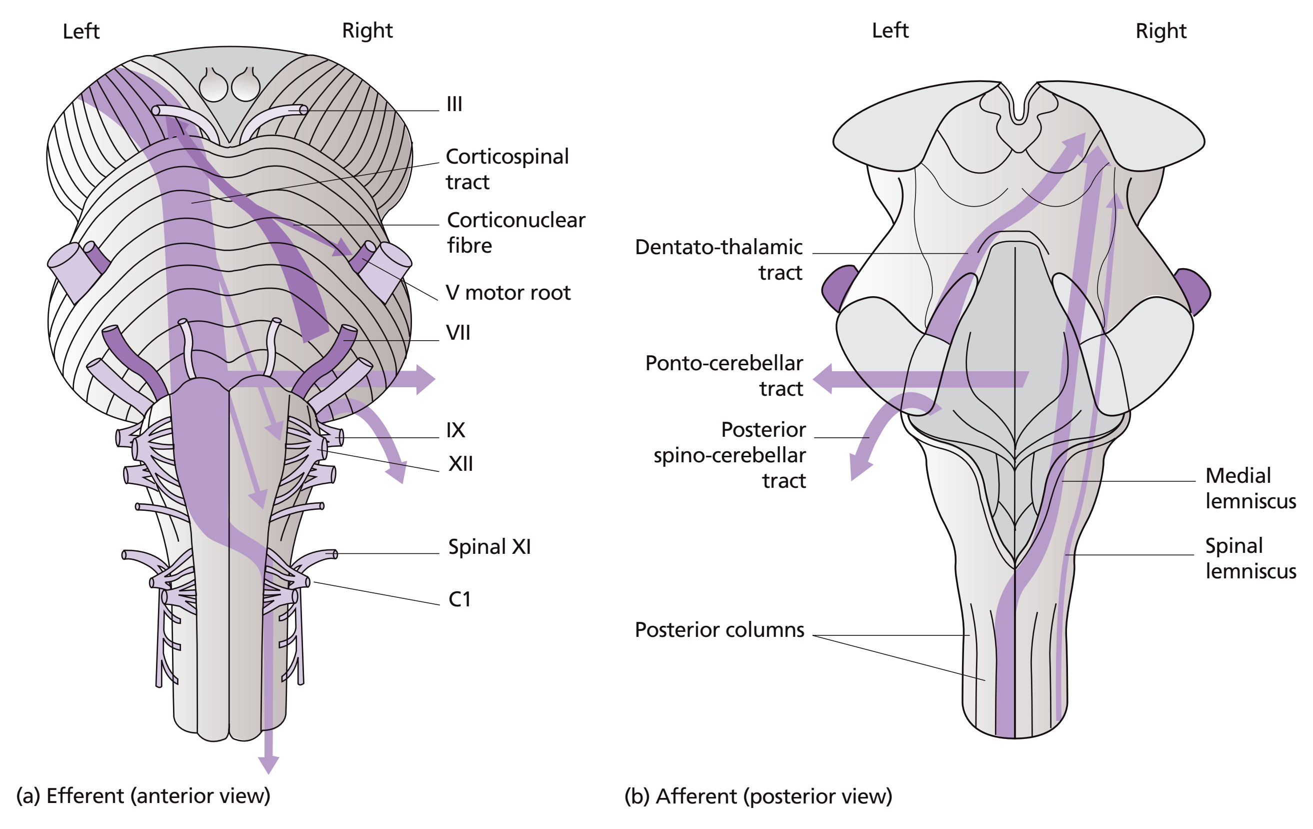
- Motor nuclei V (mastication muscles) receive 50% of fibres from each cerebral hemisphere: an internal capsule stroke usually causes no perceptible jaw deviation.
- Nuclei VII are supplied differentially, i.e. upper facial nuclear neurones are supplied 50 : 50 from each hemisphere (cf. V) and lower facial neurones are innervated by crossing fibres. Thus, lesions of the UMN facial motor pathway spare the upper face, i.e. the familiar fact that a unilateral stroke causes lower facial weakness.
- IX, X, XI, XII motor nuclear neurones (in nucleus ambiguus and hypoglossal nucleus) are supplied variably by cortico-bulbar fibres in different individuals, i.e. sometimes 50 : 50, sometimes more unilaterally:
- Following an internal capsule stroke, there is usually no unilateral palate, tongue or vocal cord weakness, i.e. innervation is 50 : 50 from each side;
- When unilateral deviation of the tongue is seen after a hemiparesis, it is simply that the supranuclear innervation of the XIIth nucleus is largely contralateral. There is no need to consider an additional lower motor neurone (nuclear) brainstem lesion (see Pseudo-bulbar palsy, Chapter 12).

The hypoglossal nuclei also receive projections from the RF (see motor nuclei of V and supratrigeminal nuclei below), cortical speech areas and cerebellum.

The situation for XI causes confusion. Uncrossed supranuclear fibres innervate XIth nuclear neurones for sternomastoid of the same side. Other supranuclear fibres cross to innervate XIth nuclear neurones for trapezius on the opposite side.

Clinical correlates (XI nerve)

In the normal person, as the left hand reaches out (right motor cortex, left anterior horn cells), the head turns (logically) to the left. This head turning is achieved by the right sternomastoid,



(a) Efferent (anterior view)

(b) Afferent (posterior view)

Figure 2.20 Brainstem main efferent (a) and afferent (b) pathways.

innervated ipsilaterally. With a left hemiparesis (e.g. right internal capsule stroke), it is this, the right, ipsilaterally innervated sternomastoid that is weak. Trapezius weakness (shoulder shrugging) is on the same side as the limb weakness in a hemiparesis.

Sensory pathways within the brainstem

The two sensory systems traverse the brainstem, to merge just before entering the thalamus:

- *Spinothalamic tracts:* pain and temperature sensation (spinal lemniscus);
- *Posterior (dorsal) columns:* light touch, two-point discrimination, light touch, kinesthesia (medial lemniscus)

Matters are then complicated by the massive Vth nuclei and their connections.

Spinothalamic tracts

Cell bodies are in dorsal root ganglia of the cord. Spinothalamic fibres cross the midline in the cord (within one to three segments of their point of entry) to form each spinothalamic tract. This ascends from the cord and comes to lie laterally in the medulla (with LL fibres lateral to UL fibres) until it merges with the medial lemniscus (ribbon-like structure) in the upper midbrain. Close to the spinothalamic tracts in the brainstem lie the descending sympathetic pathways.

Clinical correlate. A spinothalamic lesion in the brainstem causes loss of pain and temperature in the opposite limbs; an ipsilateral Horner's syndrome is also frequently present.

Posterior column → medial lemniscus

Cell bodies lie in the cuneate (UL) and gracile (LL) nuclei in the medulla. Axons decussate there and form the medial lemniscus. This ascends and rotates in the brainstem, maintaining LL fibres laterally and UL fibres medially, to coalesce with the spinothalamic tract (see above).

Vth nerve central pathways

The massive Vth nerve input enters the brainstem in the mid pons. Touch sensation and the corneal reflex afferents pass to the pontine Vth nucleus, and decussate to the opposite Vth pontine nucleus. Pain and temperature afferents enter the pons, but not the pontine Vth nucleus itself. They descend alongside the spinal Vth nucleus, enter the nucleus when they reach the medulla and upper cord and then decussate, to synapse on the opposite Vth spinal nucleus. The quinto-thalamic tract (or secondary, ascending tract of the Vth nerve) completes the route to the thalamus for nociceptive and temperature information as the trigeminal lemniscus, the ribbon-like tract lying lateral to the medial lemniscus.

Clinical correlates

The corneal reflex is the most subtle sign of an emerging Vth nerve lesion (see Chapter 3). Peripheral Vth nerve lesions are usually recognizable from symptoms and signs within the cutaneous distribution of the divisions of the trigeminal nerve, V_1, V_2 and V_3. Central lesions affecting the spinal nucleus of V produce circumoral sensory loss (see onion skin distribution, see Figure 2.51, and Chapter 12). Facial numbness on one side with spinothalamic sensory loss in the contralateral limbs is diagnostic of a dorsolateral brainstem lesion. This crossed sensory loss can occur with a lesion anywhere between upper cervical cord and mid pons. When a cavity develops within the medulla (see syringobulbia below), bizarre patterns of facial and upper cervical sensory loss can be seen when the crossing central fibres of the spinal nucleus of V and quinto-thalamic tract are damaged. These are often dismissed initially as non-organic.

At a more general level, with such a magnitude of afferent information, Vth nerve sensation is highly sensitive and easily triggered. Trigeminal-mediated pain is exquisitely painful – consider toothache, trigeminal neuralgia and subarachnoid haemorrhage. The importance of the trigemino-vascular system in headaches is considered in Chapter 11.

Cranial nerve nuclear columns

A summary of the embryological development begins to explain the layout (Figure 2.21). Seven nuclear columns (four afferent, three efferent) contribute to the nuclear masses of the brainstem and cord. Motor cranial nerve nuclei are derived from two of these columns:

- III, IV, VI and XII arise from a paramedian nuclear mass known as the general somatic efferent (GSE) column; and

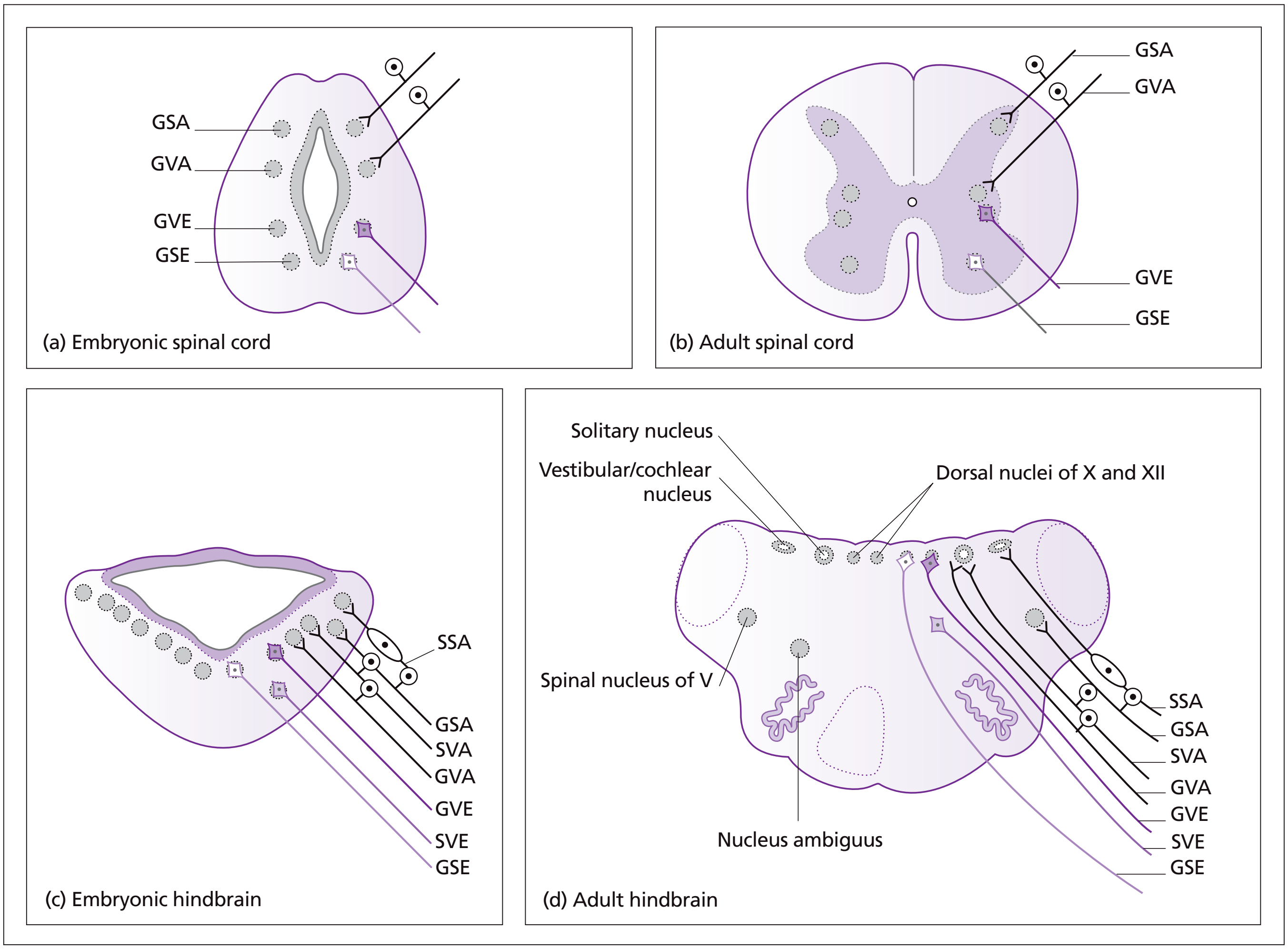

GSA
GVA
GVE
GSE
(a) Embryonic spinal cord
GSA
GVA
GVE
GSE
(b) Adult spinal cord
SSA
GSA
SVA
GVA
GVE
SVE
GSE
(c) Embryonic hindbrain
Solitary nucleus
Vestibular/cochlear nucleus
Dorsal nuclei of X and XII
Spinal nucleus of V
Nucleus ambiguus
SSA
GSA
SVA
GVA
GVE
SVE
GSE
(d) Adult hindbrain

Figure 2.21 Seven nuclear columns of the embryonic brainstem and cord. GSA, General somatic afferent; GSE, General somatic efferent; GVA, General visceral afferent; GVE, General visceral efferent; SSA, Special somatic afferent; SVA, Special visceral afferent; SVE, Special visceral efferent.

- V (motor), VII, IX and X (nucleus ambiguus) and XI (spinal accessory nucleus) arise from ventro-lateral cells known as the special visceral efferent (SVE) column.

As the fetus develops GSE column nuclei III, IV, VI and XII remain close to the midline. The SVE nuclei move laterally along the lateral margin of the fourth ventricle.

Of the main afferent nuclei:

- The Vth nerve nuclei are described in some detail (see below);
- The vestibular nuclei (SSA) occupy a wide area in the pons, extending through the medulla to upper cervical cord (see below);
- The nucleus of the tractus solitarius (SVA) receives taste fibres and relays gustatory reflexes.

Functions

The intricacies of brainstem function are hard to summarize in a few paragraphs. One approach is to consider that phylogenetically the brainstem was, very largely, the brain of distant invertebrate ancestors. The reticular formation connected olfaction to reflex movement associated with alertness, respiration, autonomic function and feeding, and hence survival. As more advanced life forms developed, cranial nerve nuclei developed to subserve more specialized sensory functions, e.g. vision and hearing. With the emergence of cerebellum and cortex, the brainstem became by default the conduit, for all axonal impulses to and from those higher destinations, adding to its complexity.

Reticular formation

The biological role of the RF can be understood from its origins as a polysynaptic, slow conducting, central pathway that:

- Linked olfactory and limbic systems;
- Co-ordinated autonomic and reflex activity.

Phylogenetically, as vision and hearing assumed important roles together with olfaction, direct, lateralized pathways of these special senses bypassed the RF. In mammals, the older pathways were superceded by fast direct linkages between cortex and sensorimotor systems.

In humans, the RF means the polysynaptic, modulating, neuronal network within the brainstem, although the system extends further – caudally into the cord and rostrally to thalamus and hypothalamus. It is of importance in:

- Respiratory control;
- Sleep, wakefulness, arousal and mood;
- Cardiovascular control;
- Pattern generation of some reflex motor activities, e.g. chewing, swallowing, conjugate gaze;
- Micturition, bowel and sexual function;
- Sensory modulation (see Gate control below, and Chapter 22); and
- Autonomic and reflex activity generally.

Aminergic neurones are prominent in the RF:

- Serotoninergic RF neurones form a ubiquitous network throughout the raphe nuclei;
- Dopaminergic neurones occupy substantia nigra and ventral tegmental nuclei;
- Noradrenergic neurones are congregated in the locus caeruleus (floor of fourth ventricle) and through the pons, medulla and midbrain;
- Adrenergic neurones occupy principally the medulla;
- Enkephalins are also involved (peri-aqueductal grey matter).

Essential anatomy

This is outlined in Figure 2.22. The raphe nuclei (raphe: Greek = seam, pronounced 'raffay') are the major source of serotinergic neurones in the neuraxis.

Alongside the median raphe nuclei lie the paramedian RF (magnocellular and gigantocellular neurones) on each side. Each paramedian network blends into the lateral RF (parvocellular neurones).

The lateral RF is largely afferent, receiving input from all sensory pathways, especially:

- Olfactory system (via median forebrain bundle, next to the hypothalamus);
- Visual pathways (via superior colliculus);
- Auditory pathways (via superior olivary nucleus);
- Vestibular pathways (via medial vestibular nucleus); and
- Somatic sensory and trigeminal system (spino-reticular tracts, pontine Vth nuclei).

The paramedian RF is a smaller efferent polysynaptic distributive pathway to:

- Thalamus;
- Spinal cord (via pontine and medullary reticulo-spinal tracts); and
- Cardiovascular and respiratory regulators.

Functions

The wide range of RF function is outlined below. There is no overriding central function, in the sense that there is no recognisable clinical condition that affects the RF as a whole. However, changes within the RF have prominent effects, principally on respiratory control, sleep and wakefulness, cardiovascular control, patterns of primitive movement and sphincters and mood. These are outlined here.

Respiratory control

This is achieved via:

- Dorsal and ventral respiratory nuclei;
- Medullary chemosensitive area; and
- Carotid chemoreceptors.

Cyclical automatic respiration is modulated by the dorsal and ventral respiratory nuclei in the medulla. The dorsal nucleus is mainly inspiratory (efferent connections to respiratory muscles) and the ventral, expiratory. A third medial paracentral nucleus adjacent to the locus caeruleus is involved in initiating and driving respiratory rhythms. The dorsal respiratory nucleus receives excitatory impulses from the medullary chemosensitive area. These cells in the lateral RF at the level of the IXth nerve

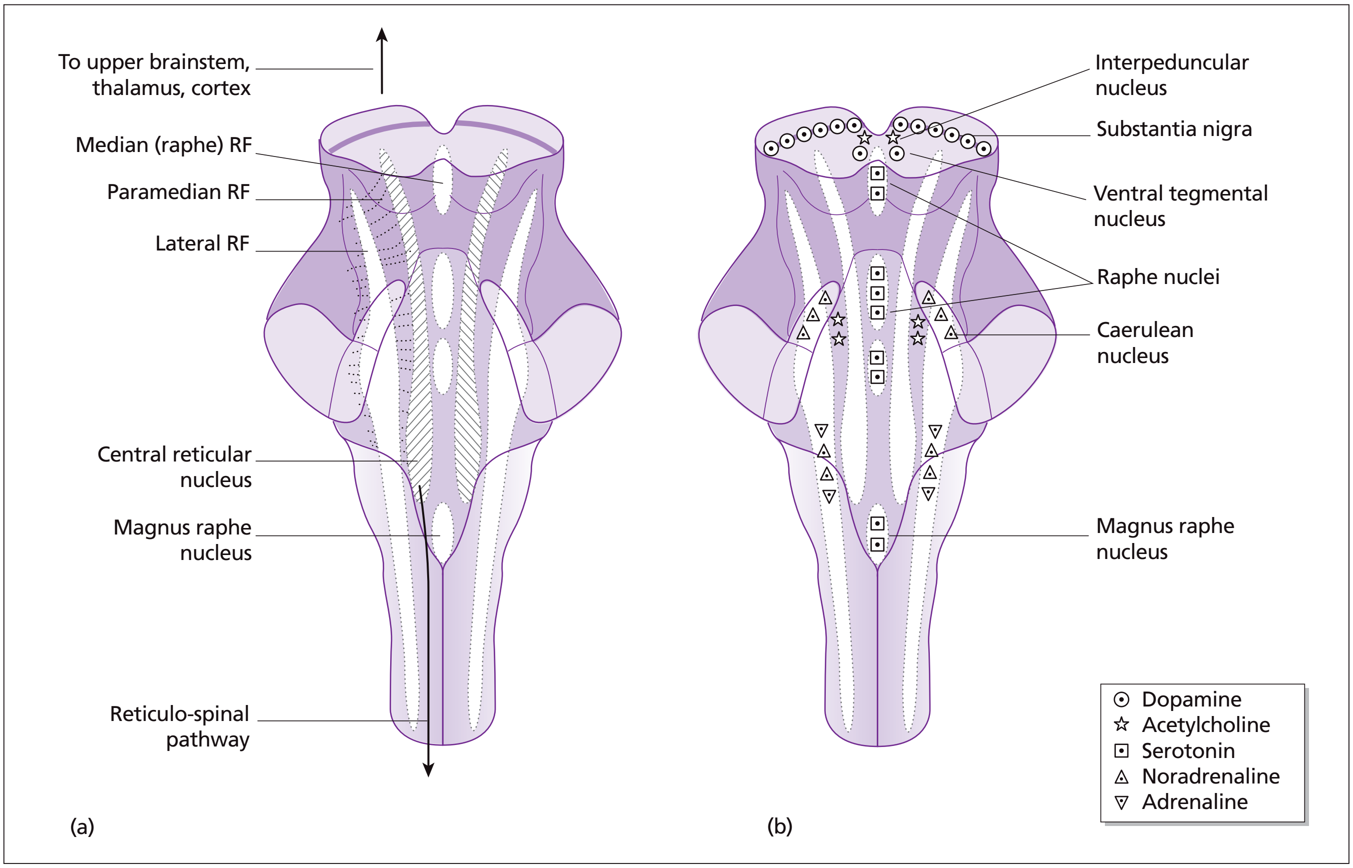

To upper brainstem, thalamus, cortex
Median (raphe) RF
Paramedian RF
Lateral RF
Central reticular nucleus
Magnus raphe nucleus
Reticulo-spinal pathway
(a)
Interpeduncular nucleus
Substantia nigra
Ventral tegmental nucleus
Raphe nuclei
Caerulean nucleus
Magnus raphe nucleus
(b)
⊙ Dopamine
☆ Acetylcholine
⊡ Serotonin
△ Noradrenaline
▽ Adrenaline

Figure 2.22 Reticular formation. (a) Subdivisions (nuclei); (b) Principal neurotransmitter cell groups.

nucleus and 4th ventricle choroid plexus are exquisitely sensitive to H^+ ion concentration. Sampling of pCO_2 takes place here: any increase in H^+ ion concentration stimulates the dorsal respiratory nucleus.

Carotid chemoreceptors (glomus cells at the carotid bifurcation) are also exquisitely sensitive to changes in arterial pO_2, and/or a rise in arterial pCO_2. Impulses pass via the sinus nerve (a branch of IX) to stimulate the dorsal respiratory centre.

The ventral respiratory nucleus is largely expiratory. It acts as an inhibitory oscillator during normal breathing and is engaged via GABAergic internuncials with the dorsal respiratory nucleus. During increased ventilation (e.g. exercise) the ventral respiratory nuclei activate anterior horn cells supplying expiratory accessory and abdominal muscles.

Sleep, wakefulness and mood

In animal models, destruction of raphe midbrain neurones or depletion of serotonin results in prolonged insomnia. The ascending reticular activating system is the term used to harness this concept of activation of the cortex by the RF. This effect is seen on EEG during arousal from sleep – high amplitude slow (delta) waves are replaced by fast (alpha) waves. The principal cellular candidates for this role are:

- Cholinergic neurones near the caerulean nuclei; or
- Histaminergic neurones in the tubero-mamillary nuclei.

Following arousal the waking state (and EEG activity) appears to be sustained by continuing activation by these neurones and by activation of the basal nucleus of Meynert in the basal forebrain. As a corollary, inactivity within the ascending reticular activating system is inherent in the mechanisms of coma.

The limbic system and RF are mentioned in Chapter 21 and the orexin-hypocretin system in Chapter 19.

Cardiovascular control

The solitary nuclei in the medulla receive afferents from baroreceptors in the carotid sinus and aortic arch. The barovagal and barosympathetic reflexes modulate blood pressure and cardiac output (Chapter 23).

Patterns of primitive movements

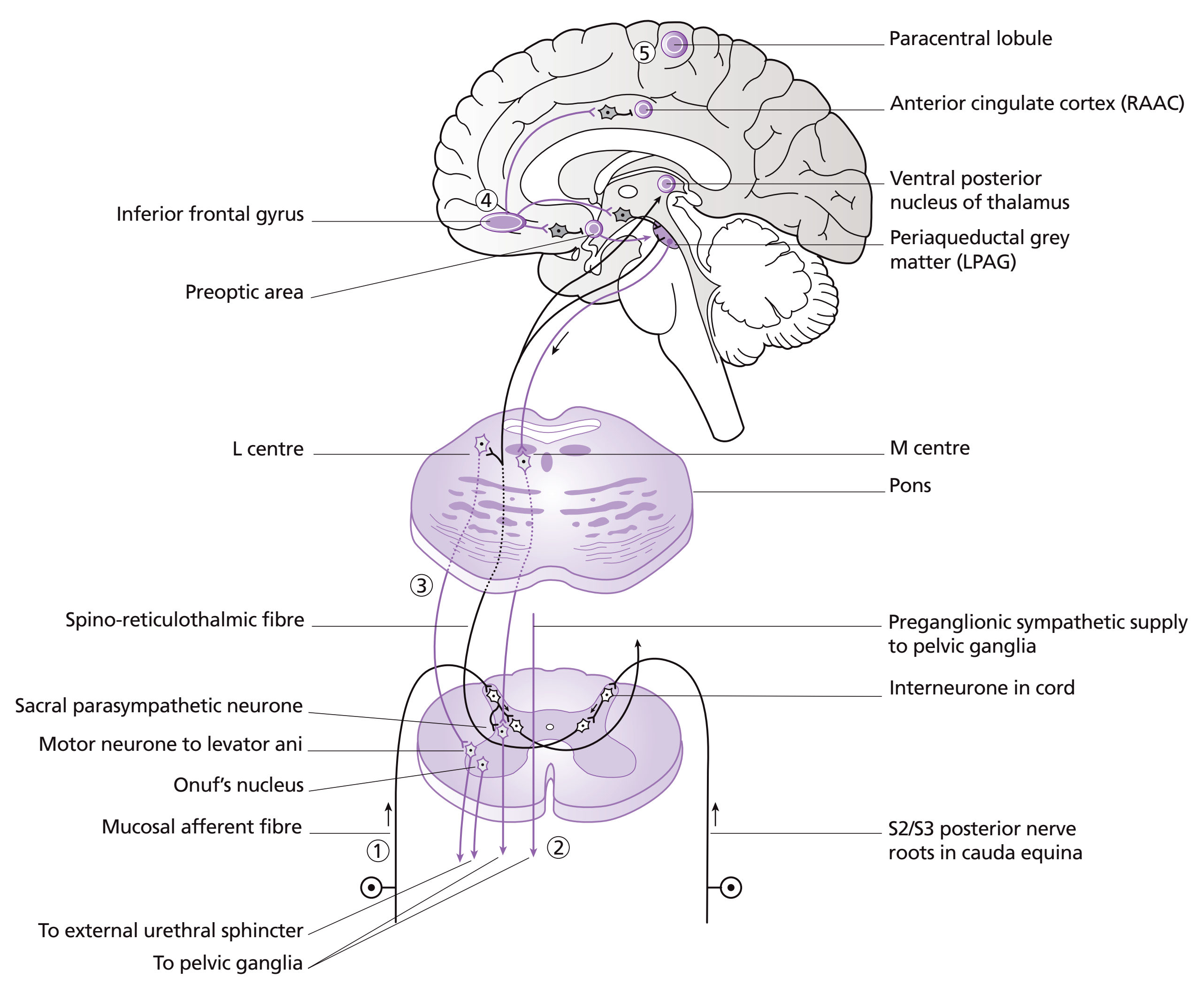
- Conjugate gaze – pontine centres for lateral and vertical gaze;
- Chewing – supratrigeminal premotor pontine nucleus;
- Respiration – medullary respiratory nuclei;
- Swallowing, coughing, sneezing, vomiting, crying, salivation;
- Locomotor pattern generators.

These movements are primitive only in phylogenetic terms. They are initiated by complex rhythmical patterns of neuronal activity within the brainstem.

Micturition control

A micturition control centre (MCC or M centre) is in each paramedian pontine reticular formation (PPRF). Axons from magnocellular neurones pass directly to parasympathetic (motor) neurones at S2–4 in the cord. Stimulation of the M centre in the PPRF produces a rise in intravesical (bladder) pressure and relaxation of the external sphincter. The latter is brought about by excitation of GABAergic interneurones from the L (lateral) centre in the PPRF. These pass to and synapse in Onuf's nucleus in the cord (parasympathetic motor innervation of the bladder muscles). The bladder begins to empty.

The essential anatomy of cortical and subcortical influences on normal micturition are included here (Figure 2.23). Neurones in lateral (right) peri-aqueductal grey matter (LPAG) receive fibres



Paracentral lobule
Anterior cingulate cortex (RAAC)
Ventral posterior nucleus of thalamus
Periaqueductal grey matter (LPAG)
Inferior frontal gyrus
Preoptic area
⑤
④
L centre
M centre
Pons
③
Spino-reticulothalmic fibre
Preganglionic sympathetic supply to pelvic ganglia
Interneurone in cord
Sacral parasympathetic neurone
Motor neurone to levator ani
Onuf's nucleus
Mucosal afferent fibre
①
②
S2/S3 posterior nerve roots in cauda equina
To external urethral sphincter
To pelvic ganglia

Figure 2.23 Neuroanatomy of micturition control:
1 As intravesical pressure increases, bladder detrusor and trigone stretch receptors are activated (S2, 3 and 4).
2 Spino-reticular fibres relay impulses → thalamus, midbrain and pons. Right PPRF L centre, LPAG, RACC are activated.
3 Sympathetic activity increases + parasympathetic activity inhibited. Bladder compliance increases. Bladder continues to fill.
4 Spino-reticular fibres via PPRF L centre activate the Onuf's nucleus (sacral cord). External sphincter tone increases: micturition is prevented.
5 Urgency is perceived when bladder becomes full. If time and/or place are unsuitable, the inferior frontal gyrus becomes activated, RACC is suppressed. M centre, LPAG and PON are suppressed.
6 Voluntary micturition is accomplished, when appropriate, by M centre activation → relaxation of the external sphincter accompanied by increase in intravesical pressure/active (voluntary) contraction of abdominal muscles.

from the sacral posterior grey horn and project excitatory fibres to the M centre. The ventral posterior nucleus of the thalamus also receives sacral fibres. The LPAG also receives excitatory fibres from the pre-optic nucleus (PON).

The right anterior cingulate cortex (RACC) is activated when the bladder fills (intravesical pressure increases). The right-sided bias (not seen exclusively) is believed to be related to emotional and topographical aspects of where and when it is appropriate to micturate. The inferior frontal gyrus is activated when the time and/or place to micturate are deemed unsuitable. The LPAG, RACC and PON are inhibited.

Gate control: sensory modulation

The anatomy and role of the RF in the control of pain, better termed supraspinal antinociception, is summarized in Figure 2.24. Gating (Chapter 22) involves the control of synaptic transmission between one neurone (or set of neurones) and the next. While gating of nociceptive inputs is but a theory and still debated, it remains a useful model.

Tactile sensory transmission is probably gated at the posterior column nuclei (see above). Nociceptive transmission from the trunk and limbs is gated in the posterior grey horn of the cord, and from the head and neck in the spinal V nucleus.

The seminal structure here is the substantia gelatinosa, rich in excitatory glutaminergic neurones and inhibitory GABAergic and enkephalinergic neurones. Unmyelinated C fibres mediate dull, intense, prolonged, poorly localized pain, largely via excitatory substantia gelatinosa interneurones and thence via lateral spino-thalamic tracts to the thalamus. Short, sharp, well-localized pain is mediated by finely myelinated Aδ fibres. These synapse directly on dendrites of relay neurones of the lateral spino-thalamic tract.

Large A (mechano-receptor) afferents from hair follicles and skin synapse on anterior spinothalamic relay cells and send collaterals to inhibitory (GABAergic) gelatinosa cells. These then synapse on lateral spinothalamic tract relay cells.

Gating of C fibre activity can be enhanced by stimulating A fibre afferents (e.g. rubbing, transcutaneous electrical nerve

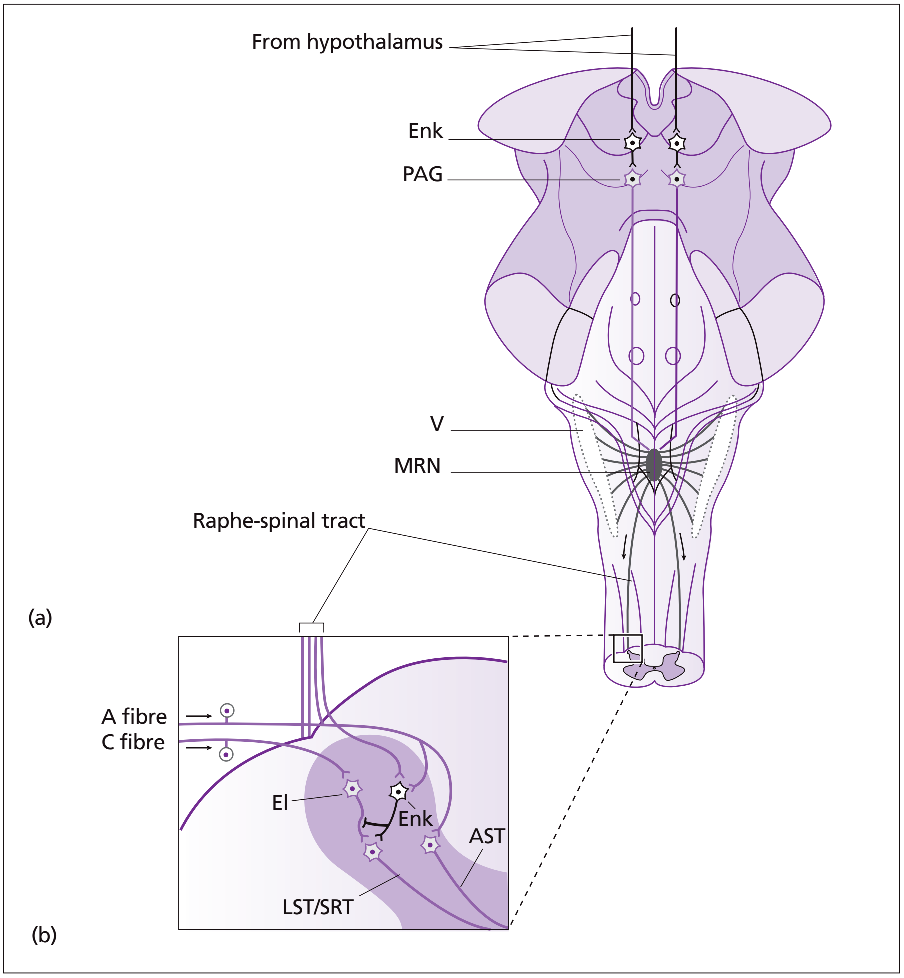


Figure 2.24 Anatomy of sensory modulation.
1 The magnus raphe nucleus (MRN) in the medulla is the origin of raphe-spinal fibres in the tract of Lissauer that synapse in the substantia gelatinosa of the cord at all levels.
2 Many RF raphe-spinal fibres are serotoninergic. They excite inhibitory interneurones in the posterior grey horn of the cord.
3 Peri-aqueductal grey matter (PAG) projects (an excitatory system) to the MRN.
4 Hypothalamic and enkephalinergic interneurones exert tonic inhibition on PAG neurones. Inhibitory impulses from the hypothalamus disinhibit (release) PAG excitatory neurones.
5 Passage of purely tactile information – into AST – is not impeded.
6 The corticospinal tracts terminate widely in the spinal dorsal horn, including the substantia gelatinosa; one of the important functions mediated by this pathway is probably supraspinal control of sensory input.

Enk: enkephalinergic interneurones
PAG: peri-aqueductal grey matter
MRN: magnus raphe nucleus;
EI: excitatory interneurones;
LST: lateral spinothalamic projection cell;
SRT: spinoreticular projection cell;
AST: anterior spinothalamic tract

stimulation [TENS]) or enhancing RF inhibition from the magnus raphe nucleus (MRN), e.g. stimulus-induced analgaesia, sleep, drugs, implanted stimulators that increase central gating of pain.

Limbic system, hippocampus and related structures

The limbus (Latin = rim) was coined by Broca in the late 19th century to describe cortex bounded by the corpus callosum. The hippocampus takes its name from Greek, originally for a horse + monster (ἵππος + κάμπος) and later a seahorse, that the hippocampus clearly resembles in coronal cross-section.

The limbic system includes:

- Hippocampi, mamillary bodies and septal area;
- Insulae, cingulate and parahippocampal gyri; and
- Amygdala – subcortical nuclear masses adjacent to each temporal pole.

Other subcortical regions nearby are the nucleus accumbens, medial dorsal nucleus of the thalamus, hypothalamus and part of the reticular formation. The frontal cortex above the orbit (orbitofrontal), the temporal pole, the corpus callosum, choroid plexus and lateral ventricle are also neighbours (Figure 2.25).

The parahippocampal gyri are the main interfaces between hippocampi (known as allocortex) and the cerebral neocortex. The entorhinal cortex is the anterior section – area 28. This is six-layered cortex, exchanging fibres between the four neocortical association areas and the hippocampus. Each fornix, looping over the medial dorsal thalamic nucleus into the mamillary body, provides a second route between neocortex and hippocampus.

The planes, contours and nomenclature of the hippocampal formation (subiculum, dentate gyrus, hippocampus) are complex. Looking from above, imagine a horseshoe lying tilted in the floor of the lateral ventricle. One (lateral) arm is the hippocampus. The other arm twists into the loop of the fornix to follow the contour of the thalamus (Figure 2.26).

The familiar coronal cross-section of the hippocampus – the seahorse-like outline – has its head in the lateral ventricle and a tail leading to the entorhinal cortex. The dentate gyrus is surrounded by the seahorse's head.

Additional terminology comes from the ancient descriptive name for the hippocampus, Ammon's horn (Ammon = Egyptian ram deity + cornu = horn), hence cornu ammonis (CA) zones which divide the hippocampus into four (Figure 2.26). Pyramidal cells are the main cell types seen in the subiculum and hippocampus and granule cells in the dentate nucleus. Inhibitory GABAergic interneurones are present throughout the area.

In functional terms, this area of the brain is intimately involved in memory, arousal and mood – and pathologically in the genesis of epilepsy (see hippocampal sclerosis, Chapter 6). The summary that follows outlines majority views in a complex field within which there is continued debate. Much original work was derived from clinical observation in humans. Extrapolation and conjecture from primate studies, and more recently fMRI, have added new insights into the roles of these areas. Their clinical relevance in epilepsy, memory and mood – and in dementia – are dealt with in the relevant chapters (6 and 7).

Afferent hippocampal connections

The perforant path passes from the entorhinal cortex to dendrites of dentate nucleus granule cells. The alvear path passes from the subiculum to the alveus, the ventricular face of the hippocampus. Mossy fibres, the axons of granule cells synapse in CA3 pyramidal cells. CA3 pyramidal cell axons pass into the fimbria, giving rise to Schaffer collaterals between CA3 and CA1. CA1 projects to the entorhinal cortex. Visual, visuo-spatial and auditory afferents also reach the region:

- Auditory fibres from the superior and middle temporal gyri to hippocampus;
- Visuo-spatial data from area 40 (supramarginal gyrus); and
- Visual association data (object shape and colour/facial recognition) from the occipito-temporal region to the peri-rhinal cortex (adjacent to the entorhinal) and thence to the hippocampus.

Diffuse afferent connections (poorly identifiable anatomically) also reach the hippocampus (Table 2.4) largely via the fornix.

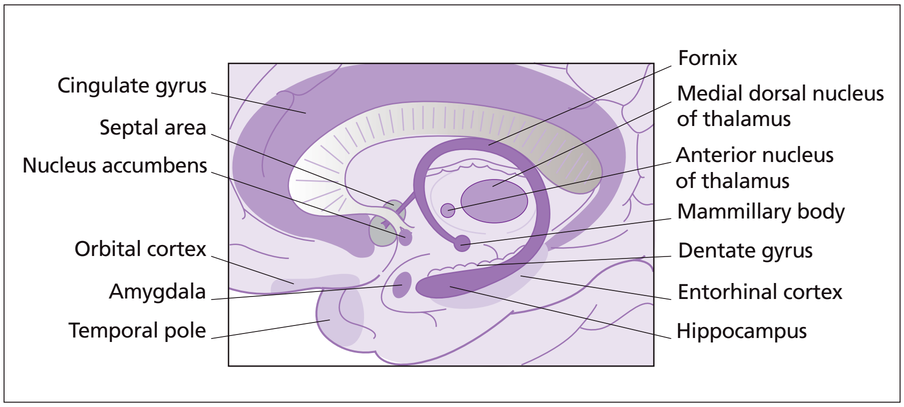
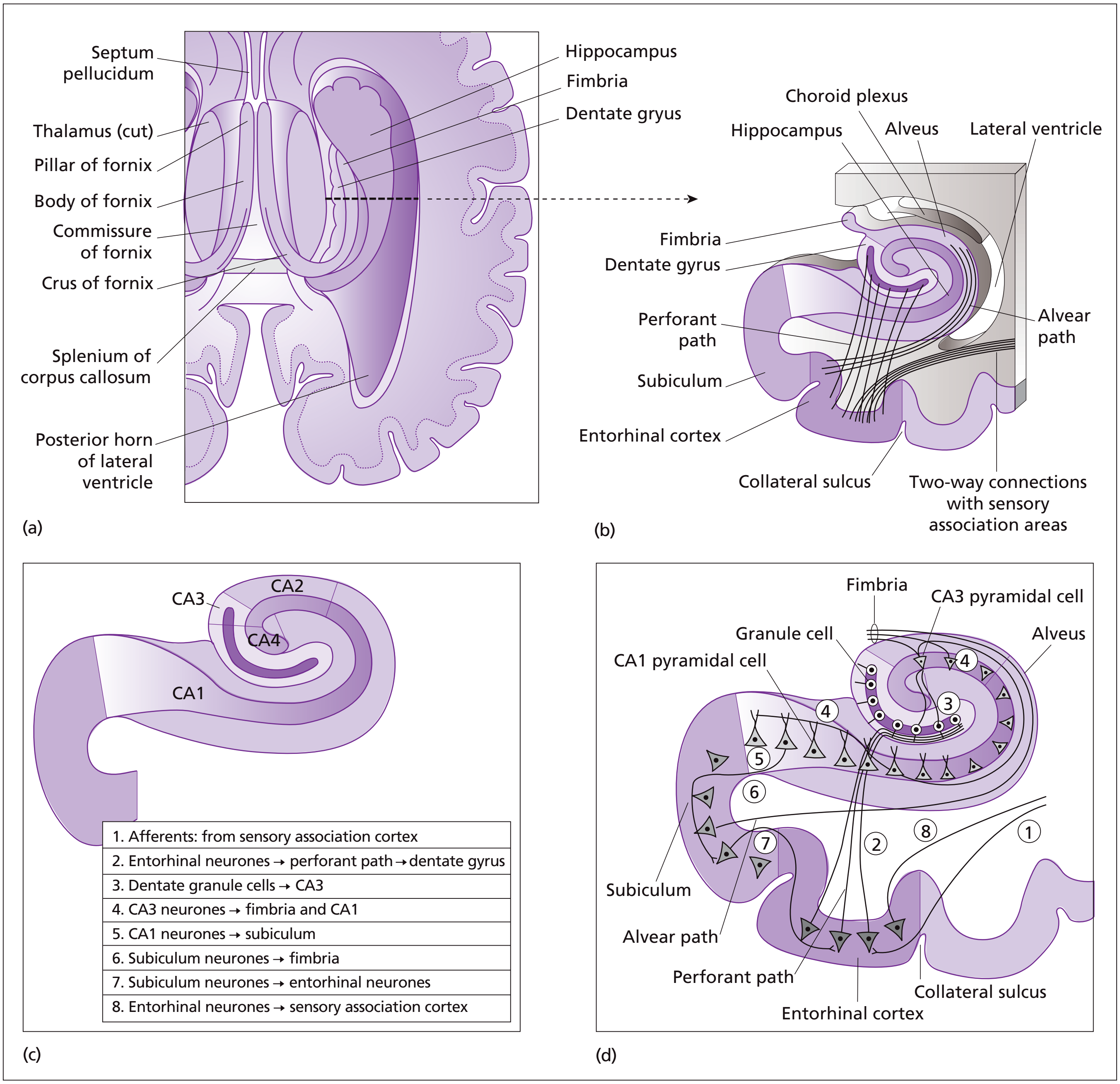


Figure 2.25 Limbic and subcortical areas: medial view.


Septum pellucidum
Thalamus (cut)
Pillar of fornix
Body of fornix
Commissure of fornix
Crus of fornix
Splenium of corpus callosum
Posterior horn of lateral ventricle
Hippocampus
Fimbria
Dentate gryus
(a)
Choroid plexus
Hippocampus
Alveus
Lateral ventricle
Fimbria
Dentate gyrus
Perforant path
Subiculum
Entorhinal cortex
Collateral sulcus
Alvear path
Two-way connections with sensory association areas
(b)
CA3
CA2
CA4
CA1
(c)
Fimbria
CA3 pyramidal cell
Granule cell
Alveus
CA1 pyramidal cell
4
3
4
5
6
7
2
8
1
Subiculum
Alvear path
Perforant path
Collateral sulcus
Entorhinal cortex
(d)

1. Afferents: from sensory association cortex
2. Entorhinal neurones → perforant path → dentate gyrus
3. Dentate granule cells → CA3
4. CA3 neurones → fimbria and CA1
5. CA1 neurones → subiculum
6. Subiculum neurones → fimbria
7. Subiculum neurones → entorhinal neurones
8. Entorhinal neurones → sensory association cortex

Figure 2.26 (a) Hippocampal formation and surrounding structures (from above). (b) Coronal section from subiculum to lateral ventricle. (c) Horn of Ammon: CA1, CA2, CA3, CA4. (d) Hippocampal wiring: basic outline:

1 Afferents: from sensory association cortex
2 Entorhinal neurones ⟶ perforant path ⟶ dentate gyrus
3 Dentate granule cells ⟶ CA3
4 CA3 neurones ⟶ fimbria and CA1
5 CA1 neurones ⟶ subiculum
6 Subiculum neurones ⟶ fimbria
7 Subiculum neurones ⟶ entorhinal neurones
8 Entorhinal neurones ⟶ sensory association cortex

Table 2.4 Diffuse afferents to the hippocampus.

Neurotransmitter	Source	Clinical association
Cholinergic	Septal nuclei	Memory
Noradrenergic	Caerulean nuclei	Arousal
Dopaminergic	Ventral tegmentum	Movement/thought disorder
Serotinergic	Raphe nuclei	Mood

Efferent hippocampal connections

First, the entorhinal cortex projects to neocortical association areas. Secondly, axons in the fornix (Latin = vault or arch) project forwards from the subiculum and hippocampus itself. Components of the fornix are:

- Fimbria (Latin: fimbriae = thin projections, forming a fringe).
- The crus (cross) arches up below corpus callosum, joins opposite the fornix to form the trunk and hippocampal commissure.
- The trunk divides into the two pillars of the fornix.

Each pillar divides around the anterior commissure:

- Precommissural fibres pass to the septal area;
- Post-commissural fibres pass to the anterior hypothalamus, mamillary body and medial forebrain bundle.

Each mamillary body (Latin: mamilla = nipple) projects to the anterior nucleus of the thalamus, thence to the cingulate cortex.

Papez's circuit (James Papez, 1937; Figure 2.27) is the loop:

Hippocampus → fornix → cingulate cortex →
entorhinal cortex → hippocampus.

This is a useful concept that has stood the test of time, although perhaps with more anatomical than clinical day-to-day relevance (Chapter 21).

Declarative memory and long-term potentiation

Data-based (declarative) memory, the ability to retain and retrieve new factual information, is lost when the anterior hippocampus is damaged. Procedural memory is preserved (e.g. how to change a wheel, thread a needle, assemble a jigsaw, ride a bicycle). The hippocampus is not involved in procedural memory – there is growing evidence that the cerebellum is the principal structure involved in these procedural or motor memories.

Long-term potentiation (LTP) is a phenomenon seen widely within the nervous system but especially within the dentate gyrus and hippocampus. As its name implies, target cells remain sensitive to a fresh stimulus a long time (hours) after stimulation.

LTP can be demonstrated in animals both in perforant path → dentate granule cells and Schaffer collateral → CA1 connections. A brief, several millisecond stimulus to either Schaffer collaterals or perforant path induces this long-lasting sensitivity in target neurones following GABA receptor activation. New synapses appear (within minutes), while older generations of synapses expand. It is believed that LTP is of fundamental importance in learning. LTP is enhanced by opioid peptides, norepinephrine and dopamine released within the perforant path.

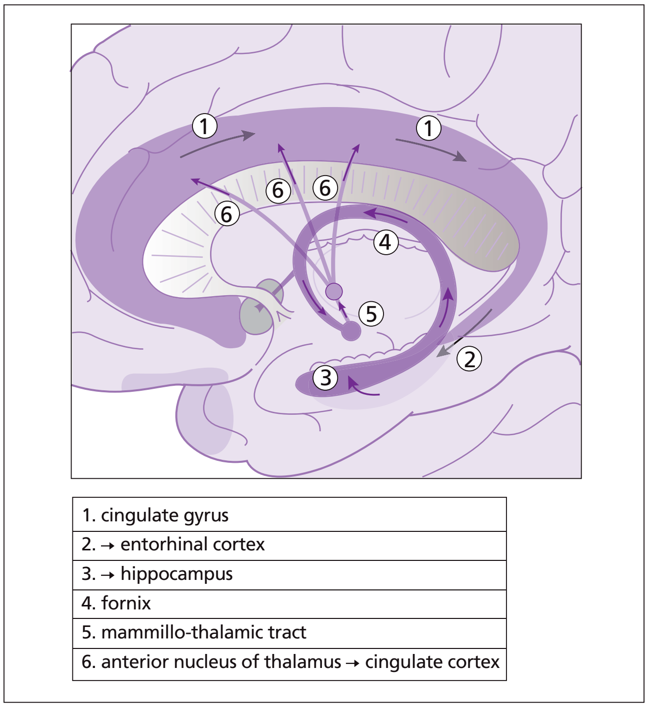

1
1
2
3
4
5
6
6
6
1. cingulate gyrus
2. → entorhinal cortex
3. → hippocampus
4. fornix
5. mammillo-thalamic tract
6. anterior nucleus of thalamus → cingulate cortex

Figure 2.27 Papez's circuit.

ACh muscarinic activity within the hippocampus is also significant in learning. Hyoscine in small doses blocks memory for lists and numbers. (Hyoscine = scopolamine, the 'truth drug' of 007, CIA and KGB repute. Recall is frequently distorted by hyoscine and hallucinogenic effects are frequent – making it of no real value for this purpose.) Physostigmine blocks the effect of hyoscine. This was the original basis for anticholinergic therapy in Alzheimer's disease.

Kindling

Clinically, the term is used (if often conjecturally) to describe development of seizure activity in a specific area of brain contralateral to or distant from an epileptic focus. At a neurophysiological level, it means a group response within neurones that increases following a uniform strength stimulus. This phenomenon is unique and, as far as is known, confined to the amygdala and hippocampus.

Insula, cingulate cortex and parahippocampal gyrus

The insula can conveniently be divided into three:

1 *Anterior:* a cortical centre for pain (on fMRI);
2 *Posterior:* connects with the amygdala and entorhinal cortex (emotional responses to and memories of pain); and
3 *Central:* possible language functions.

The cingulate cortex, part of Papez's circuit merges into the posterior parahippocampal gyrus behind the splenium. The anterior cingulate (part of the rostral limbic system – amygdala,

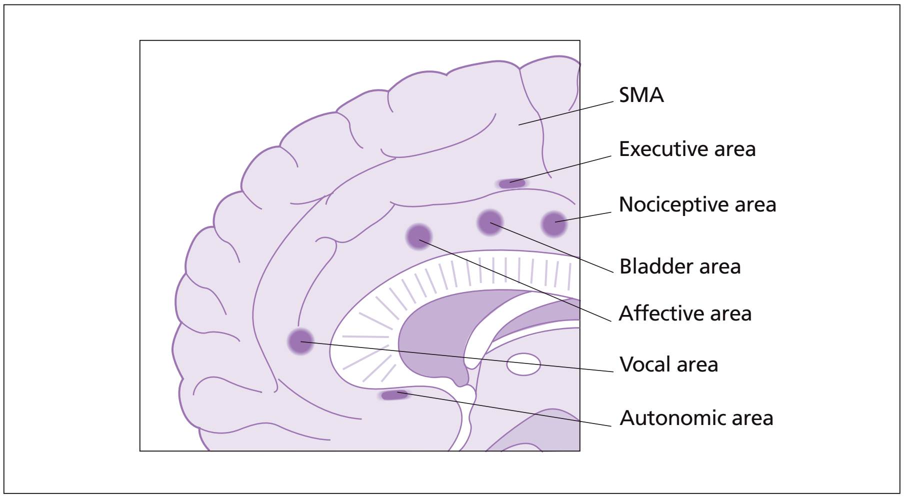


Figure 2.28 Six functional zones: anterior cingulate cortex (medial view).

ventral striatum and anterior insula) has six functional zones (Figure 2.28):

1 *Executive:* connected to dorso-lateral prefrontal cortex (DLPFC) and SMA;
2 *Nociceptive:* afferents from thalamus (medial dorsal nucleus);
3 *Affective* (emotional): happy thoughts light this area on fMRI – and the amygdala switches off. Anterior cingulectomy was once performed for aggressive psychopathic behaviour;
4 *Micturition:* activity seen on bladder filling;
5 *Vocalization:* active during decisions about syntactic construction. Reduced regional blood flow is seen in some cases of stammering;
6 *Autonomic:* respiratory and cardiac – responses to emotion, sweating and blushing.

Amygdala

Amygdala is Greek for an almond. This is a substantial nuclear group anterior to the caudate nucleus tail. Fear and anxiety are mediated via the amygdala – a glance at the afferent and efferent pathways of Tables 2.5 and 2.6 indicates the widespread connections and potential pathways for everyday experiences, e.g. feeling unwell, hypotensive and sweaty at the sight of blood.

Nucleus accumbens

Stimulation of these areas of the ventral striatum (nucleus accumbens, ventral olfactory tubercle, ventral caudate and putamen) leads typically to a sense of well-being akin to a shot of heroin, attributed to excessive dopamine release flooding the prefrontal cortex and nucleus itself. Almost every drug of abuse increases dopamine levels in these areas. Ninety-five per cent of nucleus accumbens neurones are spiny GABAergic projection neurones; 5% are cholinergic neurones (non-spiny, a.k.a. aspiny neurones).

Septal region

Afferents to the septal nuclei come from:

- Hippocampus (via fornix);
- Brainstem, via medial forebrain bundle (monoaminergic neurones);
- Amygdala, via the diagonal band of Broca; and
- Olfactory tract, via medial olfactory striae.

Table 2.5 Amygdala afferents – to the lateral nucleus.

Type	Subcortical origin	Cortical origin
Touch	VP nucleus of thalamus	Parietal cortex
Hearing	MGB	Superior temporal gyrus
Vision	LGB	Occipital cortex
Smell		Piriform lobe
Memory		Hippocampus/entorhinal cortex
Cardiac	Hypothalamus	
Pain	RF	Insula
Cognitive		Orbital (frontal) cortex
Attention/anxiety	Locus caeruleus	Basal nucleus of Meynert

LGB, lateral geniculate body; MGB, medial geniculate body; RF, reticular formation; VP, ventral posterior (nucleus).

Table 2.6 Amygdala efferents – from the central nucleus.

Pathway/distant target nucleus	Effect
PAG	Pain suppression (anti-nociception)
PAG	Freezing (in fear)
Locus caeruleus	Wakefulness/arousal
Medullary norepinephric neurones (to lateral grey horn)	Increase in pulse and blood pressure
Hypothalamus/dorsal nucleus of vagus	Slowing of pulse/syncope
Hypothalamus (corticotrophin RF)	↑ Cortisol secretion
Parabrachial (thence to respiratory) nuclei	Hyperventilation/apnoea

PAG, peri-aqueductal grey matter; RF, reticular formation.

Efferents travel in two principal pathways:

1 Striae medullaris → habenula nucleus → habenulo-interpeduncular tract → interpeduncular nucleus; and

2 Septo-hippocampal tract.

The interpeduncular nucleus participates in sleep–wake cycles (with the locus caeruleus).

The septo-hippocampal tract is believed to have a role in generating temporal cortex theta EEG activity. Synchronous discharge of hippocampal pyramidal neurones is thought to be the origin of this underlying rhythm.

Stimulation of the septal region in humans produces pleasurable sexual sensations and/or orgasm. In animals, destructive lesions have been shown to cause extreme anger – known as septal rage.

Basal forebrain

This region lies between the olfactory tract and infundibulum (caudally) and the amygdala. The magnocellular basal nucleus of Meynert is the largest single nuclear group here, its cholinergic neurones extending throughout the cortex (Figure 2.29). The basal nuclei, septal nuclei and neurones in the diagonal band of Broca are sometimes known simply as basal forebrain nuclei. The floor of the basal forebrain, the anterior perforated substance, is traversed by branches of the anterior cerebral arteries. Tonic cholinergic activity in the cortex, emanating from the basal forebrain nuclei, is concerned with maintaining wakefulness, thus facilitating perceptive activity within the cortex. Cholinergic activity is believed to enhance LTP in pyramidal cells of the cortex.

The thalamus

The paired conjoined thalami are among the larger nuclear masses of the brain. They are highly complex relay stations. In contrast to this complexity, the clinical neurology is relatively sparse, but of increasing relevance with the further development of stereotactic surgery and neurostimulation. The following is a practical clinical guide to the anatomy and function.

Divisions and connections are shown in Figure 2.30. It can be simplified by noting the large 'Y', of thalamic white matter – the internal medullary lamina – that divides the nuclei into three cell groups:

1 Anterior (within the 'Y');

2 Medial dorsal; and

3 Lateral nuclei.

Lateral nuclei are divided into ventral and dorsal tiers. The medial and lateral geniculate bodies lie posteriorly. The reticular nucleus surrounds each thalamus laterally, separated by an external medullary lamina traversed by thalamo-cortical fibres. The three functional groups of thalamic nuclei (somewhat uninformatively named) are:

1 Relay (specific) nuclei;

2 Association nuclei; and

3 Non-specific nuclei.

Principal connexions are shown in Table 2.7.

Cortical connections

Four, largely afferent connections from thalamus to cortex run in the anterior, posterior, inferior and superior thalamic peduncles in a cruciform arrangement:

1 The anterior thalamic peduncle reaches the cingulate gyrus and prefrontal cortex via the internal capsule (anterior limb).

2 The superior thalamic peduncle reaches the motor, premotor and sensory cortex via the internal capsule (posterior limb).

3 The posterior thalamic peduncle reaches the occipital, posterior parietal and posterior temporal lobes (also via internal capsule).

4 The inferior thalamic peduncle reaches the anterior temporal and orbital cortex.

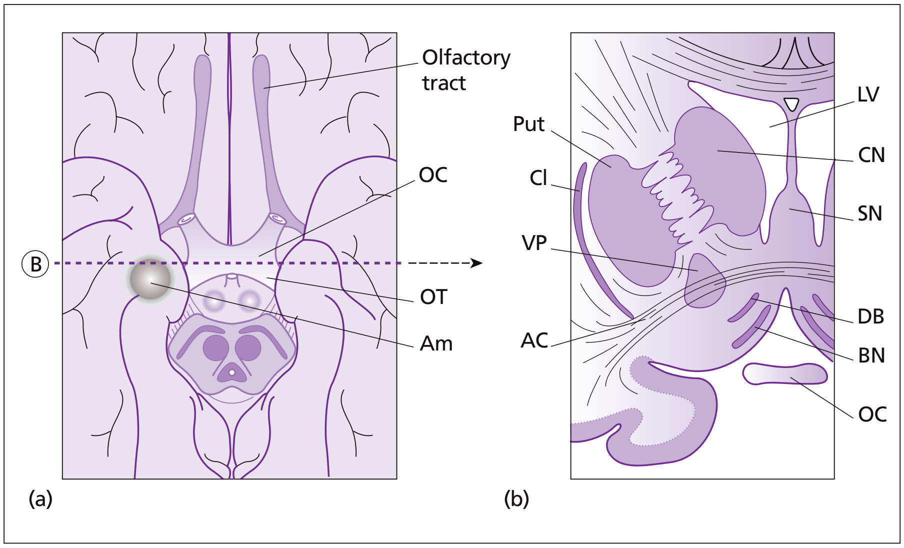


Figure 2.29 (a) Basal view of forebrain. AC, anterior commissure; Am, amygdala; BN, basal nucleus of Meynert; Cl claustrum; CN, caudate nucleus; DB, diagonal band of Broca; LV, lateral ventricle; OC, optic chiasm; OT, optic tract; SN, septal nucleus; VP, ventral pallidum. (b) Basal forebrain nuclei. (Coronal section at Ⓑ.)

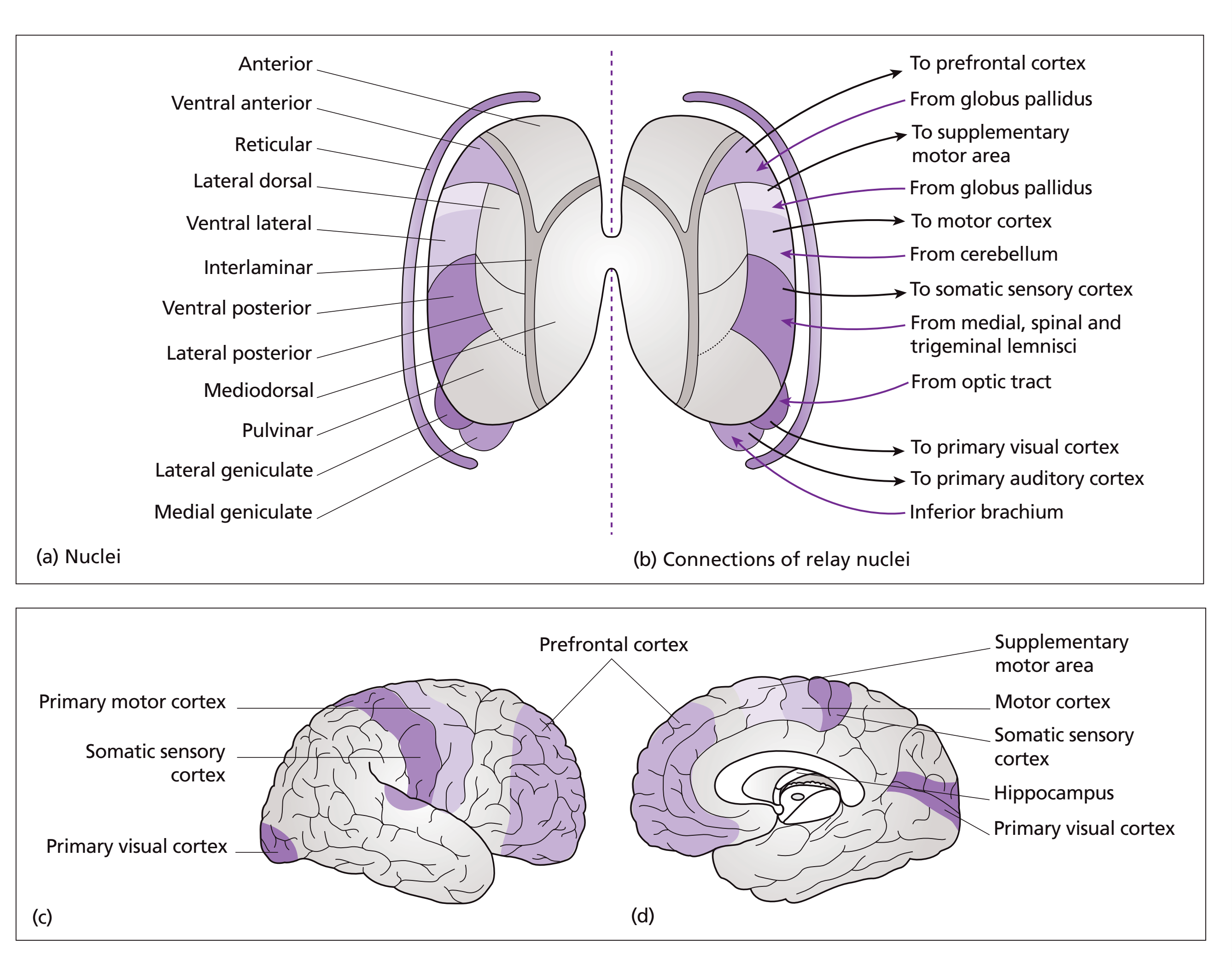

Anterior
Ventral anterior
Reticular
Lateral dorsal
Ventral lateral
Interlaminar
Ventral posterior
Lateral posterior
Mediodorsal
Pulvinar
Lateral geniculate
Medial geniculate
(a) Nuclei
To prefrontal cortex
From globus pallidus
To supplementary motor area
From globus pallidus
To motor cortex
From cerebellum
To somatic sensory cortex
From medial, spinal and trigeminal lemnisci
From optic tract
To primary visual cortex
To primary auditory cortex
Inferior brachium
(b) Connections of relay nuclei
Prefrontal cortex
Primary motor cortex
Somatic sensory cortex
Primary visual cortex
(c)
Supplementary motor area
Motor cortex
Somatic sensory cortex
Hippocampus
Primary visual cortex
(d)

Figure 2.30 Thalamic nuclei and connections (from above). (a) nuclei; (b) connections of relay nuclei; (c) hemisphere – lateral view; (d) hemisphere – medial view.

Table 2.7 Thalamic nuclei: sources and destinations of fibres.

Source	Thalamic nucleus	Destination
Mamillary body	Anterior	Cingulate gyrus
Globus pallidus	VA	Prefrontal cortex
Globus pallidus	VL (anterior)	Supplementary motor area
Cerebellum (dentate nucleus)	VL (posterior)	Motor cortex
Head somatic afferents	VPM	Somatic sensory cortex (S1)
Trunk + limb somatic afferents	VPL	Somatic sensory cortex (S1)
Inferior colliculus (auditory)	Medial geniculate body	Primary auditory cortex
Superior colliculus (vision)	Lateral geniculate body	Primary visual cortex
Parietal lobe	Lateral dorsal	Cingulate cortex
Superior colliculus + parietal lobe	Pulvinar + lateral dorsal	Visual association cortex
Reticular formation	Intralaminar	Cortex – many areas
Thalamus	Reticular nucleus	Thalamus

VA, ventral anterior nucleus; VL, ventral lateral nucleus; VPL, ventral posterior nucleus, lateral; VPM, ventral posterior nucleus, medial.

Each fan of these sensory fibres forms part of the corona radiata (between the internal capsule and the cortex).

Specific (relay) thalamic nuclei

These nuclei of the ventral tier are connected to distinct motor and sensory areas of the cortex:

- Anterior and ventral anterior (VA) nucleus (Table 2.7).
- The anterior part of the ventral lateral nucleus (VL) receives fibres from the pallidum and relays them to the supplementary motor area.
- The posterior part of VL receives fibres from the opposite superior cerebellar peduncle (from the dentate nucleus) and relays to the motor cortex.
- Ventral posterior nucleus (VP). This receives all axons of the medial, spinal and trigeminal lemnisci (see below) and projects to the somatosensory cortex. The somatotopic arrangement is shown in Figure 2.31. The medial part (VPM) deals with the head; the lateral (VPL) with the limbs and trunk. Within each part of the VP there is segregation of sensory modalities – proprioception at the front, nociception at the back, with touch in the middle.
- The ventral intermediate nucleus (VIM), located between VL and VPL provides a direct route for somatosensory input to the motor cortex. VIM is of significant importance in the functional neurosurgical treatment of tremor (Chapter 5).

Within the VP there is no evidence of gating (cf. the substantia gelatinosa) or modulation – the system is either off (no pain) or on (intense pain). This perhaps helps to explain the sinister, persistent and untreatable pain of the thalamic syndrome, when a stroke disconnects VP from the sensory cortex (see Chapter 22).

- The medial geniculate body is an auditory system nucleus;
- The lateral geniculate body is a nucleus of the visual system.

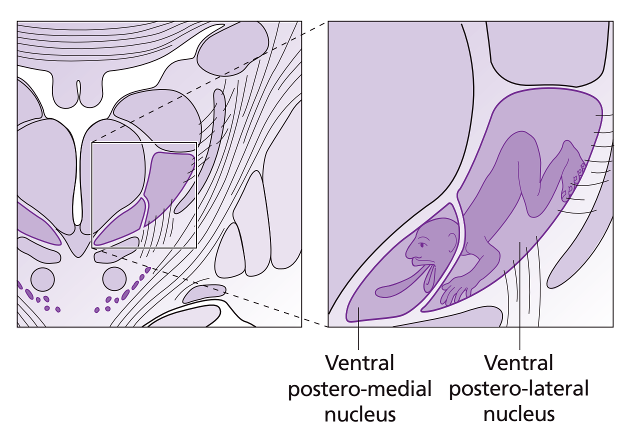

Ventral postero-medial nucleus
Ventral postero-lateral nucleus

Figure 2.31 Thalamus (coronal section): ventral posteromedial and ventral posterolateral (VPM/VPL) nuclei – postulated somatotopic projection.

Association thalamic nuclei

These are so called because they are connected to association areas of the cortex:

- The lateral dorsal nucleus is connected to the cingulate cortex (memory).
- The medial dorsal nucleus is connected to entire prefrontal cortex, olfactory and limbic systems (mood, executive function, cognition, memory, associations of smells).
- The pulvinar and lateral posterior nucleus project to the visual and parietal association cortices, having received fibres from the lateral geniculate. Also, a direct pathway, from optic tract via superior colliculus reaches the visual cortex, without relaying through the lateral geniculate – involved in attention within the visual field, but outside conscious perception.

Non-specific thalamic nuclei

These nuclei are non-specific in the sense that they are not thought to be directly involved with individual sensory modalities. The intralaminar nuclei are the rostral termination of the reticular formation. Aminergic afferents reach the region from the midbrain raphe nuclei and the locus caeruleus. Prolongation of such excitatory aminergic activity in thalamo-cortical fibres is one effect of tricyclic drugs, and a possible mode of their action in chronic pain. There is widespread onward connection from intralaminar nuclei to the cortex.

The shield-shaped reticular nucleus connects to all thalamic nuclei. Each thalamo-cortical fibre connects to a reticular nucleus neurone via a collateral. Reticular nucleus cells respond by a GABAergic inhibitory response to the corresponding thalamic nucleus – terminating a sensory stimulus (Figure 2.32). During sleep–wake cycles, thalamo-cortical neurones are constantly inhibited during sleep (consider the effect of sleep/sedation on pain) and constantly active (disinhibited) during wakefulness.

Hypothalamus

The multiple paired nuclei of each hypothalamus (about 4 g apiece in humans) lie each side of the third ventricle. They are involved in two allied neuro-effector control systems:

1. Autonomic nervous system; and
2. Pituitary axis.

In one sense the hypothalamus is a central neural effector of basic survival. Consider its role in:

- Temperature homeostasis;
- Regulation of food and water intake;
- Defence, arousal and sleep–wake cycles;
- Sexual activity.

Looked at in another way, the hypothalamus mediates central control of all endocrine and all autonomic activity.

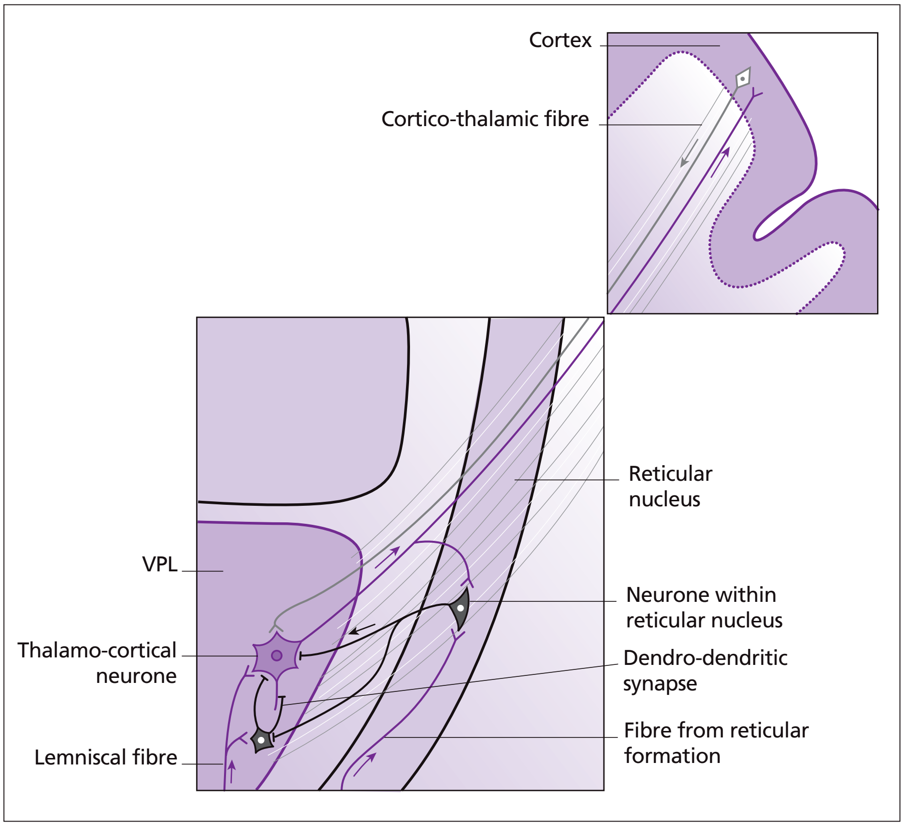


Figure 2.32 Connections from reticular nucleus of thalamus. VPL, ventral postero-lateral nucleus.

The essential nuclear anatomy is outlined in Figure 2.33 and the three groups of nuclei are listed in Table 2.8. The median forebrain bundle (aminergic fibres) merges with and lies lateral to the lateral nucleus of the hypothalamus on each side.

Arterial and capillary supply

Delicate perforating branches of the anterior communicating artery supply the hypothalamic region. Hypophyseal branches of the internal carotid artery supply the pituitary itself:

- *Superior hypophyseal artery:* anterior pituitary;
- *Inferior hypophyseal artery:* posterior pituitary.

Each hypophyseal arterial system forms a second capillary portal system that surrounds the neuroendocrine cells. Hormones are liberated into venous blood, draining into the cavernous sinus. These fenestrated portal capillaries are outside the blood–brain barrier.

Neuroendocrine cells

These neurones, cells specific to the region, both conduct action potentials and also liberate into the bloodstream peptide and other hormones, the latter having been synthesized in the endoplasmic reticulum and stored in Golgi complexes. The peptides are attached to long-chain polypeptides – neurophysins. Cell bodies of neuroendocrine cells lie in the region of the pre-optic nuclei and tuber cinereum. The principal nuclei that also contribute to this system are:

- Supra-optic;
- Paraventricular;
- Ventromedial; and
- Arcuate nuclei.

Small neurone (parvocellular) axons in the tubero-infundibular tract reach the median eminence, where releasing factors (RH) and inhibiting factors (IH) are liberated. Large neurone (magnocellular) axons form the hypothalamo-hypophysial tract that passes to the posterior pituitary.

Anterior pituitary axis

The hormones of the anterior pituitary axis will be familiar. (Table 2.9). All known RH/IHs, with the exception of prolactin IH, are peptides. Prolactin IH is dopamine. The complex control systems for these hormones, outside the scope of this chapter, include:

- Traditional feedback loops;
- Depolarization by action potentials entering from the limbic system and reticular formation (e.g. arousal effects);
- Hyperpolarization by local GABAergic neurones;
- Inhibition by opiate-releasing neurones (numerous in the hypothalamus); and
- Activation directly of anterior pituitary endocrine cells by opiates and endorphins.

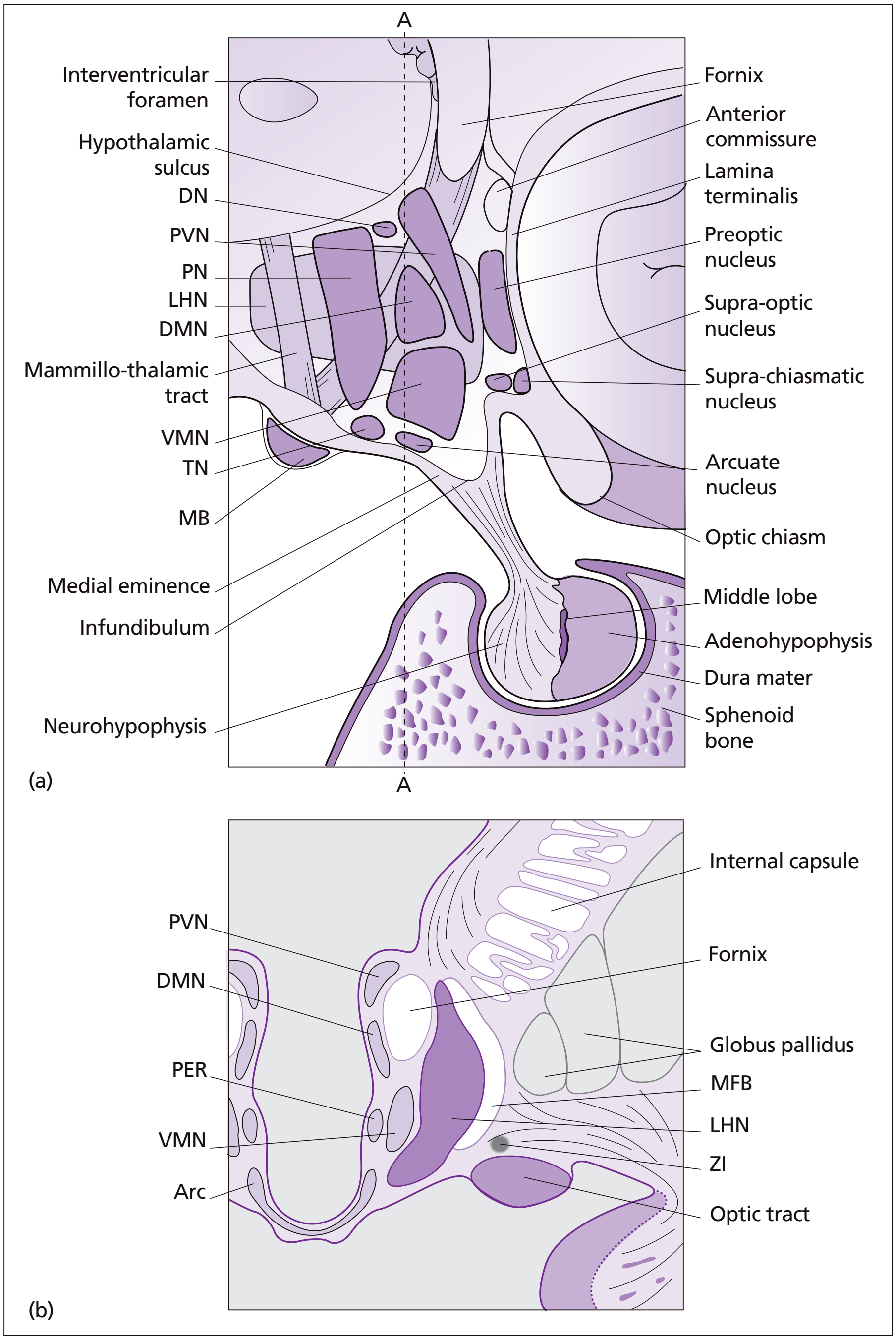

A
Interventricular foramen
Hypothalamic sulcus
DN
PVN
PN
LHN
DMN
Mammillo-thalamic tract
VMN
TN
MB
Medial eminence
Infundibulum
Neurohypophysis
Fornix
Anterior commissure
Lamina terminalis
Preoptic nucleus
Supra-optic nucleus
Supra-chiasmatic nucleus
Arcuate nucleus
Optic chiasm
Middle lobe
Adenohypophysis
Dura mater
Sphenoid bone
(a)
A
PVN
DMN
PER
VMN
Arc
Internal capsule
Fornix
Globus pallidus
MFB
LHN
ZI
Optic tract
(b)

Figure 2.33 Hypothalamic nuclei. (a) Saggital section. (b) Coronal section through A–A. Arc, arcuate nucleus; DMN, dorsomedial nucleus; DN, dorsal nucleus; LHN, lateral hypothalamic nucleus; MB, mamillary body; MFB, medial forebrain bundle; PER, periventricular nucleus; PN, posterior nucleus; PVN, paraventricular nucleus; TN, tuberomamillary nucleus; VMN, ventromedial nucleus; ZI, zona incerta.

Table 2.8 Hypothalamic nuclei.

Anterior	Middle	Posterior
Pre-optic	Paraventricular	Posterior
Supra-optic	Dorsomedial	Mammillary body
Supra-chiasmatic	Lateral	Tuberomammillary
	Ventromedial	Dorsal
	Arcuate	

Table 2.9 Pituitary and hypothalamic releasing/inhibiting hormones (RH/IH).

Anterior lobe hormone	RH/IH
ACTH	Corticotrophin RH
FSH/LH	Gonadotrophic hormone RH
Growth hormone	Growth hormone RH and IH
Prolactin	Prolactin RH and IH
Thyrotropin	Thyrotropin RH

ACTH, adenocorticotrophic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Posterior pituitary axis

Each hypothalamo-hypophyseal tract passes from large (magnocellular) neurones of the supra-optic nucleus and paraventricular nucleus to the posterior pituitary (neurohypophysis). There are also contributions from peri-ventricular neurones (opiate and peptide neurotransmission) and brainstem (aminergic) neurones.

Vasopressin (antidiuretic hormone) and oxytocin are secreted by specific neurones in both supra-optic and paraventricular nuclei, the hormones being housed in axonal secretory granules (Herring bodies) before being released into the capillary system within the posterior pituitary itself.

Circumventricular organs

This term refers to six groups of specialized neurones and glial cells adjacent to the ventricular system that have an intimate relation to fenestrated capillaries:

1. Neurohypophysis;
2. Median eminence;
3. Vascular organ of the lamina terminalis (VOLT);
4. Subfornical organ;
5. Area postrema;
6. Pineal gland.

Functions are outlined in Table 2.10.

Sympathetic and parasympathetic hypothalamic activity

Posterior hypothalamic stimulation produces noradrenergic sympathetic effects:

- Heart rate ↑;
- Blood pressure ↑;
- Pupil dilatation;
- Gut stasis.

Anterior hypothalamic stimulation produces muscarinic parasympathetic effects:

- Heart rate ↓;
- Blood pressure ↓;
- Pupil constriction;
- Peristalsis.

The axonal pathway projects from anterior and posterior hypothalamus to autonomic nuclei in the brainstem and cord – via the dorsal longitudinal fasciculus in the midbrain and pons (see below).

Temperature regulation

Thermosensitive neurones in the hypothalamus respond to core temperature changes. Spino-reticular tracts also deliver information to these hypothalamic neurones from skin thermal receptors. The autonomic effector sympathetic system alters skin blood flow and sweating via the posterior nucleus of the hypothalamus – axons pass direct to the lateral horn of the cord. Increase in core temperature is achieved by:

- Skin vasoconstriction;
- Abolition of sweating;
- Shivering/muscular activity; and
- Behavioural responses, e.g. crouching, huddling.

Hypothalamic temperature-sensitive neurones also respond to exogenous pyrogen, setting the central thermostat to a higher level, and are also involved in the production of central pyrexia (Chapter 19).

Water intake and thirst

The zona incerta, a strip of cells beside each lateral nucleus of the hypothalamus, controls thirst. Lesions of this region lead to neglect of drinking, and stimulation (in animals) to thirst and excessive water intake. Many other mechanisms also contribute to osmotic homeostasis, e.g. serum sodium and glucose levels and renal function.

Appetite

Balance in activity between the lateral and ventromedial hypothalamic nuclei constitutes, in theory at least, a satiety centre in humans. In experimental models:

- Lateral hypothalamic (feeding centre) stimulation causes overeating;
- Lateral hypothalamic destruction causes lack of interest in food;
- Ventromedial hypothalamic (satiety centre) stimulation inhibits eating;
- Ventromedial hypothalamic destruction (bilateral) causes gross obesity.

Table 2.10 Circumventricular organs.

Organ	Function	Comment
Neurohypophysis	ADH secretion	See text
Median eminence	Anterior pituitary hormone release and inhibition	
VOLT + SFO	Facilitate ADH secretion	Axons to supra-optic and paraventricular nuclei (feedback loop: low blood volume → kidney → renin → angiotensin II → VOLT/SFO → ADH)
Area postrema	Chemoreceptor (emetic) centre	Reflex vomiting (situated at obex of 4th ventricle)
Pineal gland (body)	Melatonin	Sleep–wake cycles

ADH, antidiuretic hormone; SFO, subfornical organ; VOLT, vascular organ of the lamina terminalis.

Serotoninergic activity down-regulates the appetite set point, and vice versa, selective serotonin re-uptake inhibitors (SSRIs) and other antidepressants tend to increase appetite.

Mood, sexual arousal, wakefulness and memory

Mood. Aggression or docility are features of experimental lateral/ventromedial hypothalamic imbalance. Obese animals with ventromedial lesions become aggressively enraged. Underweight, ventromedially stimulated animals are docile. Hunger stimulates arousal. The relevance of this in day-to-day human behaviour is unclear but might explain why some people become angry when they are not fed at the time they expect food.

Sexual arousal. Specific neurones (INAH3 cells) in each pre-optic nucleus are more numerous in males than in females. This is an area rich in androgen receptors, activated by testosterone and which when experimentally stimulated induces (male) sexual activity.

In females, neurones rich in oestrogen receptors are found in the ventromedial nucleus: experimental stimulation induces sexual arousal.

Wakefulness. The suprachiasmatic nucleus is involved in setting sleep–wake cycles via putative pineal gland connections.

Arousal is mediated via richly histaminergic neurones in the posterior hypothalamus (the tuberomammillary nucleus). These project widely (medial forebrain bundle, cortex, brainstem, cord). Hypersomnolence in humans is seen when the posterior hypothalamus is damaged bilaterally.

Memory. The mammillary bodies are stations on Papez's circuit (fornix → mammillary bodies → mammillothalamic tract → anterior nucleus of thalamus). Mammillary body destruction produces a dramatic amnestic syndrome.

Generally, for an area so intimately involved in activities essential for life, lesions of the hypothalamus are surprisingly unusual in day-to-day neurology. The area appears resilient. One reason may be quite simple: bilateral hypothalamic destruction is necessary to produce clinical effects.

Cranial nerves

Olfactory nerve and its cortical connections

This afferent system, more highly developed in some animals than in humans, comprises:

- Olfactory neuronal epithelium;
- Olfactory nerves;
- Olfactory bulb and tract; and
- Olfactory cortical areas and connections.

Olfactory epithelium

This epithelial layer covers about one-fifth of the upper nasal cavity. Basal stem cells, unique among neurones in mammals, transform in a regular 4–8 week cycle into fresh highly specialized bipolar neurones. These neurones lie between sustentacular (supporting) cells (Figure 2.34). Their dendrites are ciliated processes containing olfactory receptors that line the receptive area. Afferent axons traverse the cribriform plate, guided by olfactory ensheathing cells, a specialized form of glia. There are two chemosensory systems within the nasal mucosa, the olfactory system and trigeminal afferents that respond to irritants, e.g. ammonia and the sensation of coolness, e.g. of menthol; the trigeminal system is mentioned no further here.

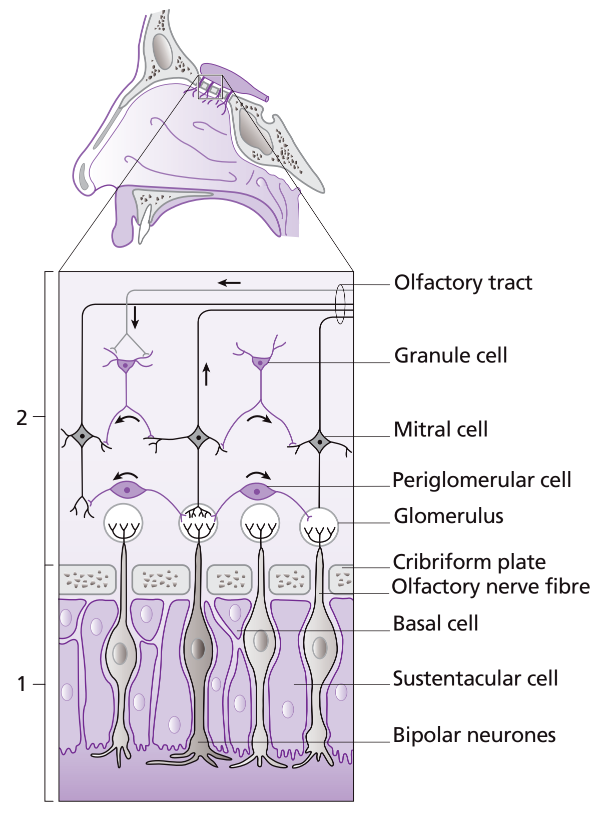


Figure 2.34 Receptor cells of the olfactory system.

Olfactory bulb and tract

Each bulb consists of some 50,000 mitral cells that make synaptic contact with epithelial bipolar neurones in several thousand glomeruli, surrounded by glia. Active glomeruli, stimulated by receptive bipolar cells, inhibit neighbouring glomeruli through a GABAergic pathway via peri-glomerular cells. Mitral cells are also under the influence of deeper granule cells, with which they make dendro-dendritic contact. Stimulated granule cells suppress other mitral cells, selectively, again via GABAergic synapses.

Cortical connections

Each afferent pathway remains entirely ipsilateral, but the anatomical tract divides in the anterior perforated substance into

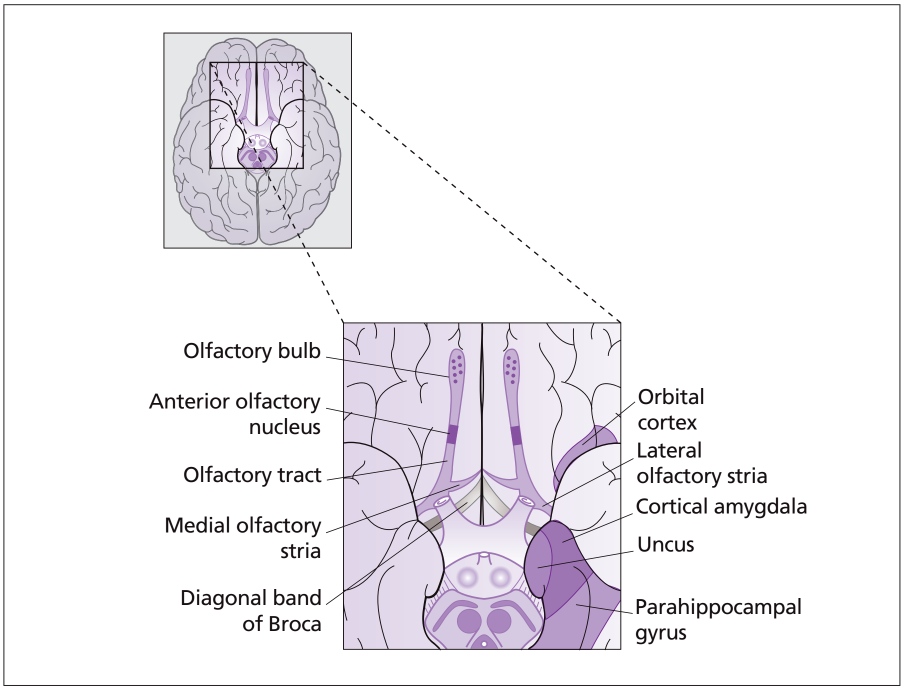


Figure 2.35 Anatomy of the olfactory tract region.

medial and lateral striae. Lateral olfactory stria afferents pass to each piriform lobe of the anterior temporal cortex (this includes part of the amygdala, uncus and parahippocampal gyrus) and thence to the posterior orbito-frontal cortex. Each medial olfactory stria contains efferent axons from each anterior olfactory nucleus – scattered neurones in the olfactory tract.

The perception and intimate complexity of different aromas is achieved by groups of cortical neurones that respond to particular sequences of action potentials. The widespread central connections of the olfactory cortex make possible association of particular smells with individual memories, both visual and topographical, recent or distant. Anosmia is discussed in Chapter 12.

Neurotransmission in the olfactory system

The practical neurology of anosmia occupies but little space in a busy out-patient clinic – and testing of discrimination of the sense of smell is frequently omitted altogether or simply accepted as normal. However, advances in the neurobiology of olfaction have broadened our understanding of this special sense and highlighted the way the cortex achieves separation and recognition of such complex afferent data.

The cilia of the bipolar neurones lining the olfactory epithelium lie at the start of a complex sequence:

- Odorant molecules bind to odorant receptor proteins;
- G-protein (G_{olf}) stimulation follows;
- Cilial adenyl cyclase is activated;
- ATP is liberated and cyclic AMP (cAMP) generated;
- Cation channels open (Na^+ and Ca^{2+}channels) →;
- → Opening of Ca^{2+}-activated Cl^- channels; and thus
- → Membrane depolarization, an excitatory action potential and propagation along the axon of a bipolar cell.

There are around 1000 odorant receptor genes. These are expressed on individual bipolar cells, i.e. there are around 1000 receptor cell subtypes, a large number, but vastly insufficient to account for the appreciation, in humans of about 100,000 different smells, or for an even more highly tuned sense of olfaction in many mammals.

In olfactory neurones, the single second messenger is cAMP, i.e. the channels are cAMP-gated. Each receptor subtype is broadly tuned – each responds to various similar odorants – and, correspondingly, each odorant can stimulate more than one receptor subtype. Thus each bipolar cell yields potentially ambiguous information. A further selection process takes place at the level of the glomeruli.

Each olfactory bulb contains some 2000 spherical glomeruli 50–200 μm in diameter. The endings of around 25,000 primary olfactory bipolar receptor axons end in the glomeruli, forming synapses with about 100 (only) second order olfactory neurones. The association between individual receptor subtypes and a particular glomerulus is precise. Receptor neurones expressing one gene, although scattered throughout the epithelium, converge on several (only) glomeruli in each olfactory bulb.

Within each glomerulus there is excitation and inhibition (e.g. see Mitral cells above) and thence it is the temporal coding of afferent impulses that determines the particular perceived smell by cortical receptive fields. Olfactory cortical neurones recognize a particular 'tune' of impulses as an individual smell.

The projection of each olfactory tract is direct to phylogenetically ancient regions of the cortex, in contrast to most other sensory input which passes first to the thalamus before reaching the cortex. From the olfactory cortex, there are projections to areas throughout the brain.

Finally, not all olfactory perception is at a conscious level. Pheromonal perception in humans undoubtedly exists – probably accounting for some part of the process of sexual attraction. Pheromones are, for example, of critical importance in lepidoptera, enabling attraction to take place over several kilometres in moths between males and females. There is evidence to support the existence of a vomero-nasal receptor organ in humans in the lateral nasal mucosa. Central pathways in humans remain unknown and the neurochemistry of pheromonal activating systems conjectural.

Optic nerve and the visual system

The visual pathway is summarized in Figure 2.36. The essential features will be familiar. This section focuses on individual aspects of this complex and highly developed special sense. Visual field defects and other clinical details are also discussed in Chapter 13.

Retinal structure

The eight retinal cell and fibre layers are shown in Figure 2.37:

- Photoreceptors (2) – rods and cones – are applied to the pigment epithelium (1), adjacent to the choroid.
- Ganglion cells (7) are the source of action potentials conducted by axons that form the retinal nerve fibre layer (8) and pass into the optic nerve.
- Two sets of retinal neurones – horizontal cells and amacrine cells – are arranged transversely.

The essential circuitary is shown in Figure 2.38.

Photoreceptors and bipolar cells

Cone photoreceptors are sensitive to bright light, colour and shape. They are clustered in and around the fovea. Photoreceptor end-feet synapse with bipolar cells and horizontal cells processes. Cone bipolar cells are either:

- ON bipolars, i.e. switched ON (depolarized) by light, or inhibited by neurotransmitters released when light levels fall. They synapse and converge on ON cone ganglion cells.
- OFF bipolars have an opposite response. They synapse and converge on OFF ganglion cells.

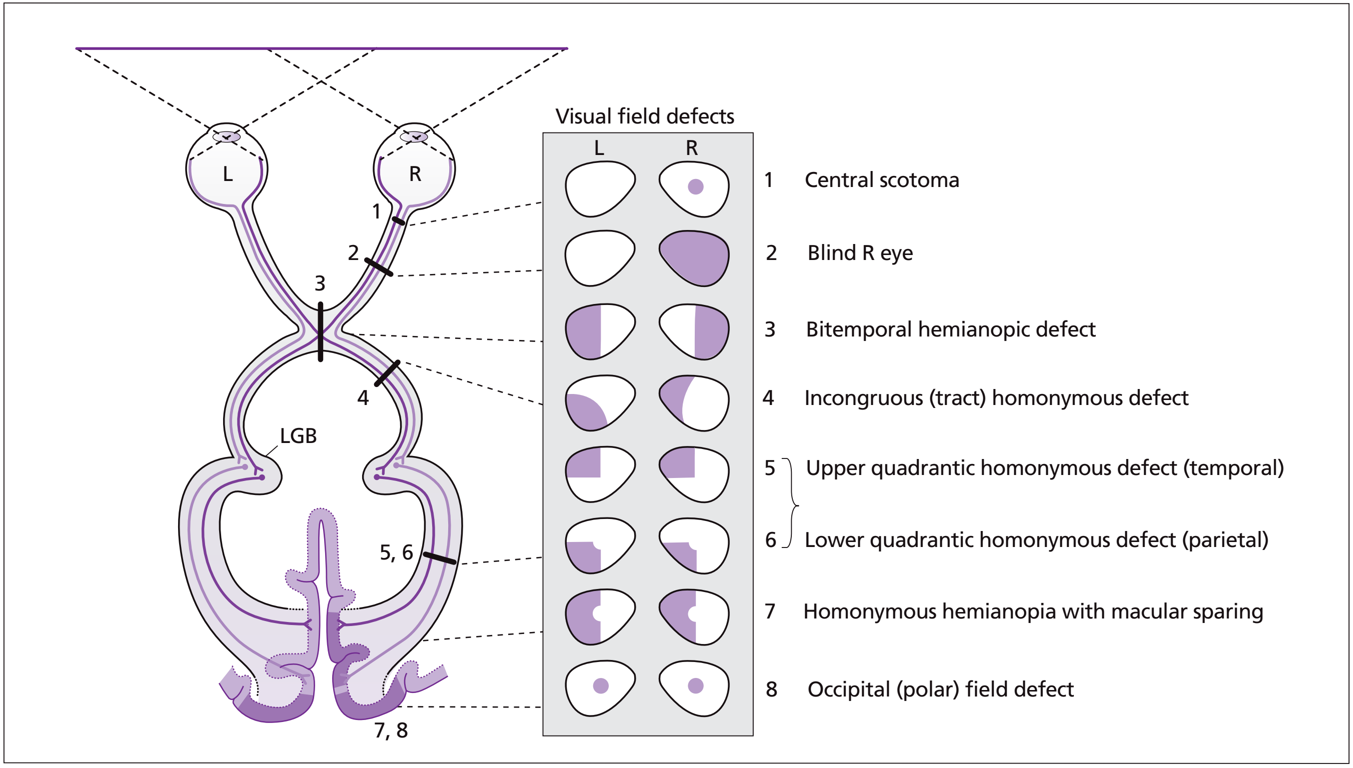

L
R
1
2
3
4
LGB
5, 6
7, 8
Visual field defects
L
R
1 Central scotoma
2 Blind R eye
3 Bitemporal hemianopic defect
4 Incongruous (tract) homonymous defect
5 Upper quadrantic homonymous defect (temporal)
6 Lower quadrantic homonymous defect (parietal)
7 Homonymous hemianopia with macular sparing
8 Occipital (polar) field defect

Figure 2.36 The visual pathway.
1,2 Optic nerve
3 Optic chiasm
4 Optic nerve
5,6 Optic radiation (temporal: lower; parietal: upper)
7 Striate cortex
8 Occipital pole
LGB, lateral geniculate body.

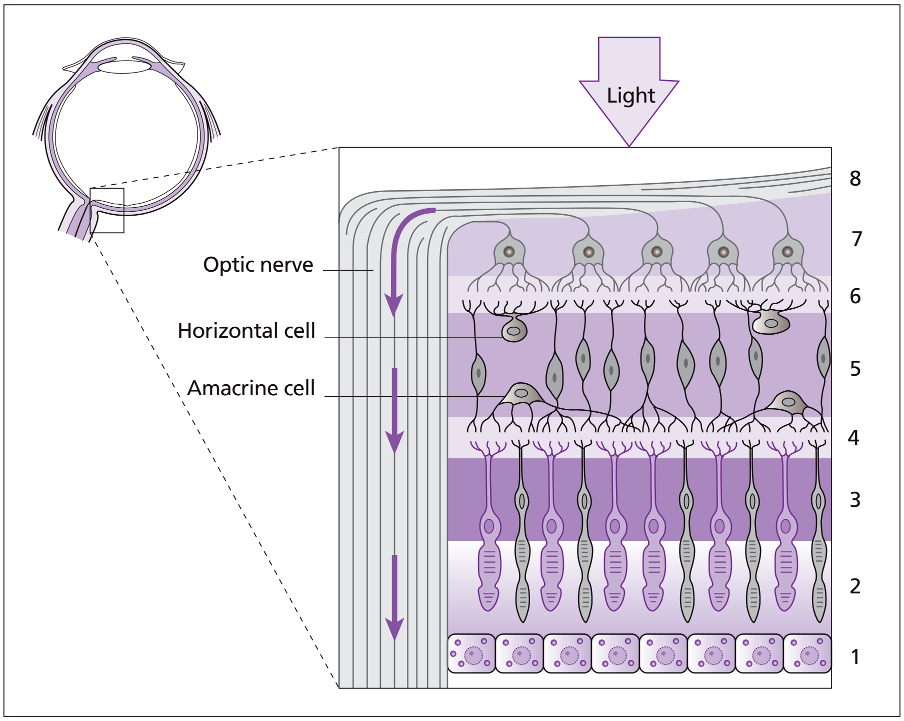


Figure 2.37 The eight retinal layers.
8 Nerve fibre layer
7 Ganglion cell layer
6 Inner plexiform layer
5 Inner nuclear layer (bipolar cells)
4 Outer plexiform layer
3 Outer nuclear layer
2 Photoreceptor layer
1 Pigment epithelium layer

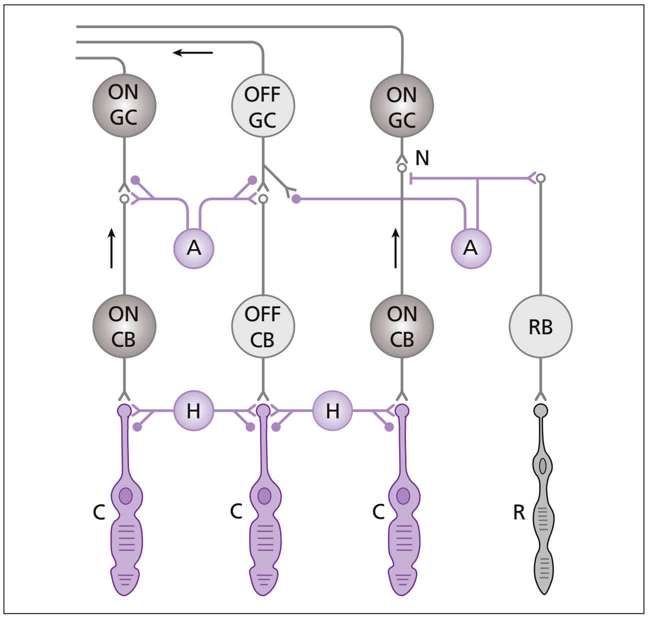


Figure 2.38 Basic circuit diagram of the retina. A, amacrine cell; C, cone; CB, cone bipolar; GC, ganglion cell; H, horizontal cell; N, nexus (gap junction); R, rod; RB, rod bipolar.

Horizontal cells extend dendrites between photoreceptors and bipolar cells with which they make inhibitory contacts. Bipolar cells (and hence retinal ganglion cells) outside the immediate zone of excitation are inhibited. This has the effect of restricting retinal activity to the area under direct photic stimulation (centre–surround antagonism).

Rod photoreceptors are active in conditions of low illumination. They are insensitive to colour – dimly lit objects are perceived in shades of grey. Like cones, rods display centre–surround antagonism, between white and black. They too synapse with ON and OFF bipolar cells.

Rod bipolar cells activate ON and OFF rod ganglion cells via amacrine cells. Amacrine cells have 6–10 dendrites that emerge from one aspect of each cell body. Over one dozen types of amacrine cell are recognized, with different transmitters, e.g. ACh, dopamine, serotonin. Their action is to modulate (turn ON or OFF) groups of ganglion cells. Visual functions include enhancement of contrast and detection of subtle movement by retinal rods.

Ganglion cells, of either ON or OFF variety, are activated by bipolar neurones. An ON ganglion cell is activated by a point light source and inhibited (via horizontal cells and appropriate bipolars) by a surrounding ring of light (annular inhibition). An OFF ganglion cell reacts in reverse fashion, being inhibited by a point source and excited by an annulus of light.

Colour recognition within the retina – red, green and blue

Colour opponency is the response that characterizes specific ganglion cells. Ganglion cells are either:

- ON-line for green + OFF-line for red;
- ON-line for red + OFF-line for green;
- ON-line for blue + OFF-line for yellow.

Colour recognition is achieved by specific individual cones because they are sensitive to particular wavelengths of electromagnetic energy.

Heterogeneity of rods, cones and ganglion cells

The majority of both rod and cone ganglion cells are parvocellular (small, P cells) – small receptive fields receptive to shape and colour. A minority are magnocellular ganglion cells (large, M cells) – large fields, particularly receptive to moving objects.

The specialized region of cones is the fovea and its central 100 µm, the foveola – the area that has the highest sensitivity for object discrimination and colour appreciation (Figure 2.39). Several anatomical features of the foveola enhance sensivity:

- Midget cones in the foveola have one-to-one synaptic contacts with midget bipolar cells and ganglion cells (outside the foveola sensitivity is less acute);
- Superficial layers of the retina have long neurites, the cell bodies being dispersed around the fovea rather than covering the cones – this allows light to strike midget cones directly.

Optic nerve, chiasm and optic tract

Each optic nerve (a CNS structure rather than a peripheral nerve) contains between 800,000 and 1.5 million ganglion cell axons, with a supporting infrastructure – astrocytes, oligodendrocytes, blood supply and meningeal sheath. The chiasmal decussation, optic tract and optic radiation are illustrated in Figure 2.40.

Each optic tract (comprised of uncrossed temporal-half and crossed nasal-half retinal axons) divides into a medial and a lateral root. The medial root of each optic tract enters the midbrain. It carries:

- Fibres serving the pupillary light reflex – passing to the pretectal nucleus;
- Fibres from retinal M cells – scanning movements – to the superior colliculus;
- Fibres to the reticular formation (parvo-cellular) – arousal function; and
- Fibres relaying from superior colliculus, to pulvinar and visual association cortex – the extra-geniculate visual pathway.

The axons of lateral root of the optic tract synapse in the lateral geniculate body (LGB) of the thalamus. The LGB is six-layered:

- Three cellular laminae receive crossed fibres and three uncrossed;
- The two deepest laminae (magnocellular) receive axons from retinal M ganglion cells (movement detection);
- The four outer laminae are parvocellular, receive axons from P ganglion cells (detail and colour).

Optic radiation

The optic radiation (syn. geniculo-calcarine tract), its ordered somatotopic arrangements and cortical targets are shown in Figure 2.40. The radiation is the most prominent white matter bundle in the posterior part of the brain. Important anatomical features are as follows:

- The radiation enters the posterior (retrolentiform) part of the internal capsule, runs beneath the temporal cortex and alongside the posterior horn of the lateral ventricle.
- Meyer's loop – forward-sweeping fibres in the anterior temporal lobe. These are from the upper part of the visual fields and run to the lower half of the occipital cortex.

Occipital cortex

The optic radiation is seen macroscopically as a pale stripe (stria) of myelinated fibres within the primary visual or striate cortex (Brodmann area 17) before synapsing with spiny stellate cells of cortical layer IV. Francesco Gennari (1752–1797) was a medical student in Padua when he described the occipital striae that bear his name.

The spiny stellate ganglion cells are arranged in alternating ocular dominance columns (alternating inputs between left and right eyes). Thus, impulses from identical points on each retina arrive in the striate cortex in side-by-side columns. Further differentiation is achieved by a hierarchy of cell groups:

- Spiny stellate cells produce simple responses – to fine slits of light in a particular orientation.
- Some pyramidal cells produce complex responses – to broad slits (bars), orientated at a particular angle and either stationary or moving broadside in one direction across the visual field.
- Other pyramidal cells are hypercomplex, responding to L-configurations.

The mechanism of this hierarchical system is explained by convergence:

- Several simple cell axons converge on to complex cells; and
- Complex cell axons converge on to hypercomplex cells.

The primary visual cortex can be thought of as a complex pixellated screen, detecting position in the visual fields, shape and movement. Area 17 (V1) does not interpret what we perceive to be vision – i.e the area does not 'recognize' a face or describe an object. Recognition, i.e. perception is achieved by connections with the visual association cortex, with the temporal lobes and memory circuits. The value of vision is also enhanced by eye movement, and by moving the head, limbs and/or trunk in relation to visual stimuli. The cortical eye fields are intimately involved in these processes.

Visual association cortex and V1–V5 terminology

Brodmann areas 18 and 19, also known as peri-striate or extrastriate (syn. visual association) cortex contain cortical cell columns concerned with feature extraction. This means that certain cell groups respond to geometry (i.e. shape), some to perception of height/depth (stereopsis) and others to colours with the ability to differentiate between many hues. The regions contain cell groups that recognize these particular attributes of objects. Afferents arrive primarily from area 17. There are also direct thalamic projections from the pulvinar.

The V1–V5 nomenclature, based more on functional imaging findings than the descriptive anatomy of the older (Brodmann)

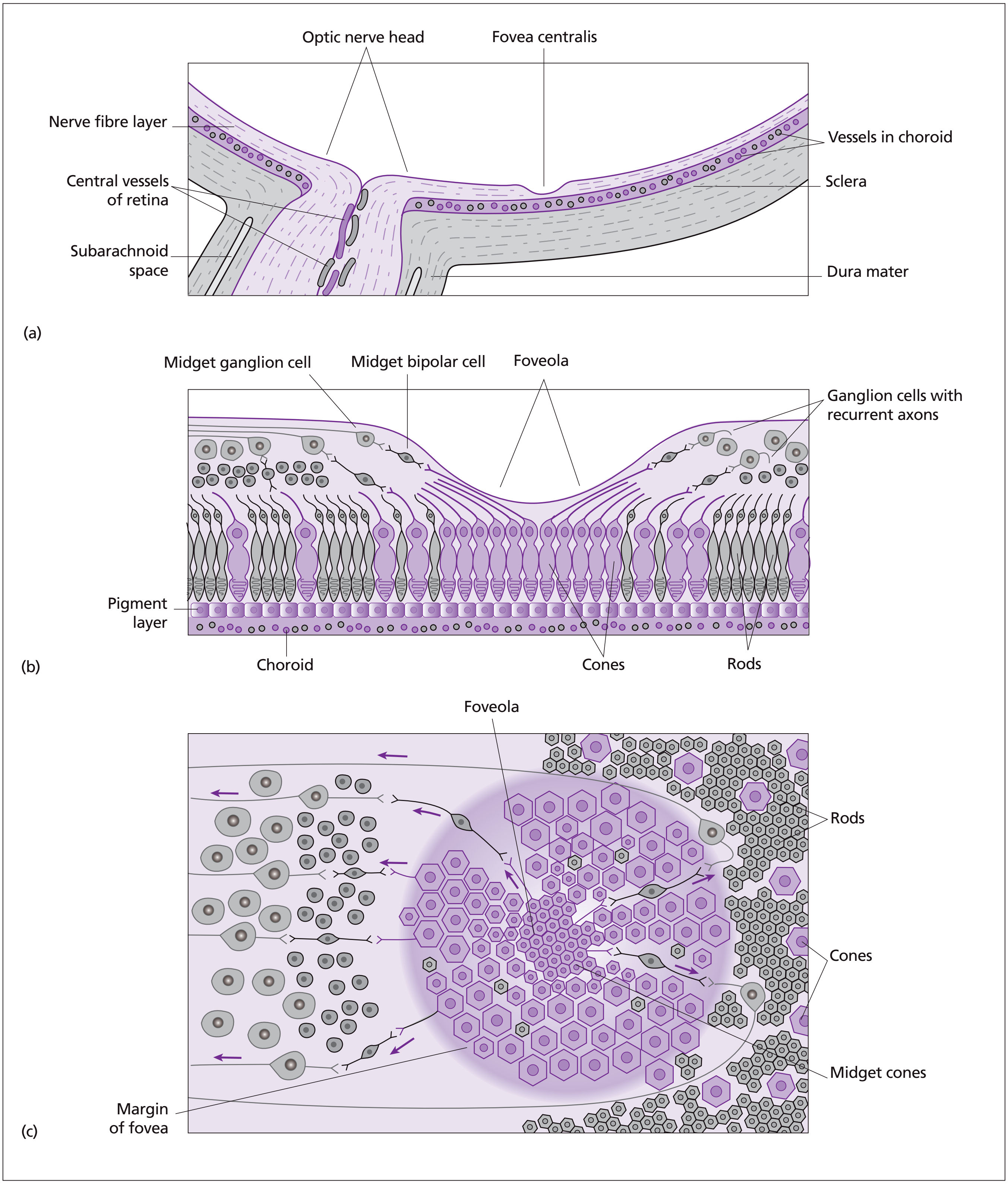

Optic nerve head
Fovea centralis
Nerve fibre layer
Vessels in choroid
Central vessels of retina
Sclera
Subarachnoid space
Dura mater
(a)
Midget ganglion cell
Midget bipolar cell
Foveola
Ganglion cells with recurrent axons
Pigment layer
(b)
Choroid
Cones
Rods
Foveola
Rods
Cones
Midget cones
Margin of fovea
(c)

Figure 2.39 The fovea. (a) Horizontal section through the optic disc and fovea. (b) Fovea and foveola. (c) Fovea and foveola (surface diagram).

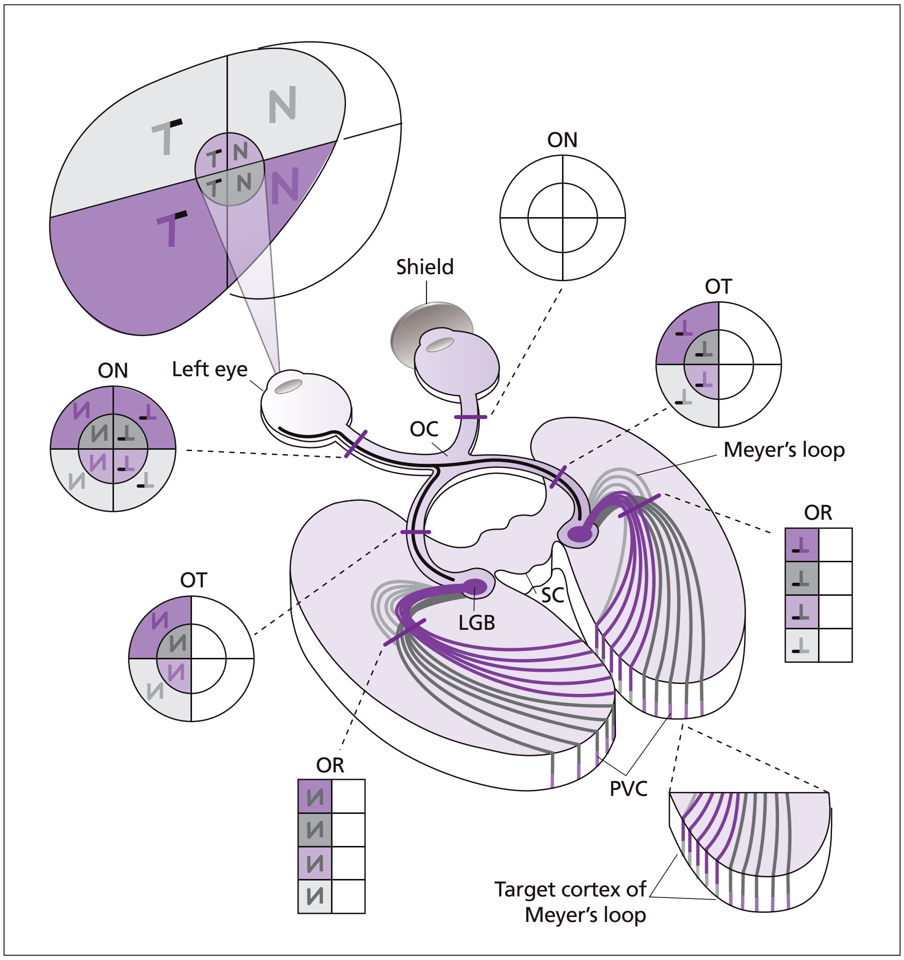


Figure 2.40 Optic nerve chiasm and optic radiation. Temporal field of left eye to primary visual cortex. LGB, lateral geniculate body; N, nasal; OC, optic chiasm; ON, optic nerve; OR, optic radiation; OT, optic tract; PVR, primary visual cortex; SC, superior colliculus; T, temporal. Note: inversion of visual field, Meyer's loop, lateral geniculate body. Foveal axons travel in lateral portion of fan of fibres within optic radiation, to reach occipital pole (posterior part of primary visual cortex).

system, is now widely used (Table 2.11). The lateral and medial parts of area 19 (V4, V5) contain specialized connections sometimes known as 'where and what' visual pathways:

- 'What' is the ventrally placed, medial stream of object recognition (V4);
- 'Where' is the lateral, dorsally situated stream concerned with location (V5), with projections to the posterior parietal lobe.

'What'

Three principal types of visual recognition take place in this region:

1 Recognition of forms, shapes and categories of objects (generic or canonical identification) takes place in the lateral zone.

2 Human face recognition (generic identification – 'this is a face') takes place in the mid zone.

3 Colour recognition takes place medially (Figure 2.41).

More sophisticated recognition of individual objects and faces involves area 20 (inferotemporal cortex) and area 38 (temporal pole cortex). Objects and faces that are threatening generate activity (via areas 20 and 38) in the amygdala and inferofrontal cortex.

'Where'

The lateral part of area 19 is particularly responsive to movement in the contralateral hemifield (Figure 2.42). The main projection is to area 7 (posterior parietal cortex), long known as the area affected in disorders of spatial recognition (e.g. astereognosis, see Chapter 3). Area 7 is involved in:

- Movement perception;
- Stereopsis (three-dimensional vision);
- Spatial sense (relative position of objects to each other).

Area 7 also receives fibres from the pulvinar ('blindsight fibres'). Fibres project to the ipsilateral frontal eye field and premotor cortex. Functional imaging shows increased cortical activity in area 7 in response to a moving object in the contralateral hemifield (covert attention). During saccadic gaze and/or limb movement towards the object both area 7 and area 5 are activated (overt attention).

Cortical eye fields

Conjugate eye movement is controlled by discrete regions within the grey matter. These are shown in Plate 2.3, Table 2.12. The complexity is evident. fMRI has been of value here, not only confirming clinical data, but also variability between individuals.

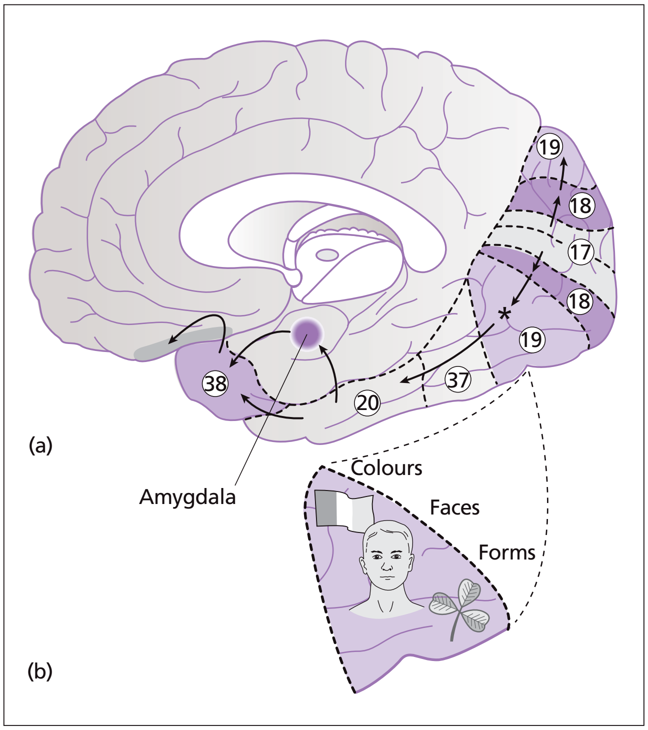


Figure 2.41 'What' visual pathway – medial surface of right hemisphere. (a) Asterisk indicates area for identification (fusiform gyrus) in left visual field. (b) Detail of ventral portion of area 19 – colours, faces and forms.

Table 2.11 V1–V5 and Brodmann areas: primary visual and visual association cortex.

V Region	Brodmann area
V1	Brodmann area 17
V2	Brodmann area 18
V3	Brodmann area 19
V4	Identification modules in fusiform gyrus in area 19 (antero-medial)
V5	Movement dedection modules in area 19 (antero-lateral)

Three different mechanisms are involved in driving conjugate, i.e. yoked (Latin: jugum = a yoke) gaze:

- *Scanning:* saccades, i.e. rapid movement from one target to another;
- *Tracking:* smooth pursuit of a target across the visual field;
- *Compensation:* maintenance of gaze during head movement via vestibulo-ocular (fixation) reflex.

Voluntary saccades are initiated in the frontal eye fields. Smooth pursuit movements originate in the occipital and parietal cortices (Table 2.12). Velocity detectors in the upper pons receive information via the medial root of the optic tract. Fixation is achieved by visual pursuit modulated by input from the vestibular system (head and neck movement) and smooth ocular movements by the cerebellar flocculus.

Automatic scanning movements are generated by retinal action potentials in the medial portion of the optic tract, via the pulvinar and area 7. These are also influenced by the cerebellar vermis and

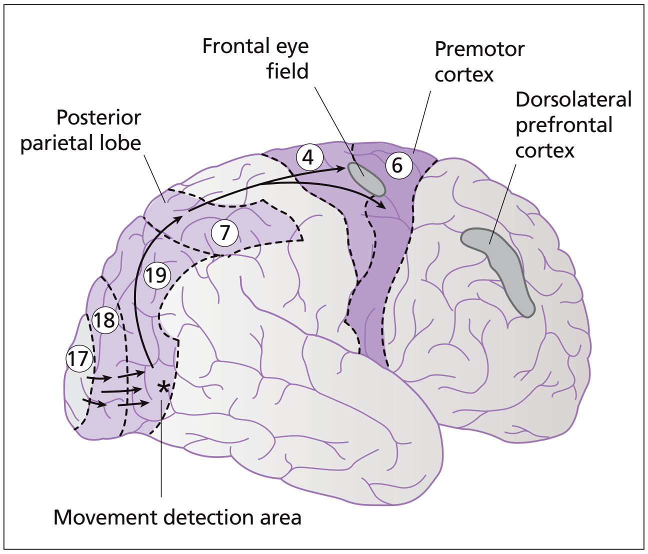


Figure 2.42 'Where' visual pathway – lateral surface of right hemisphere. Asterisk indicates area for movement detection in left visual field (Area 19). R, frontal cortical eye field activates conjugate saccades towards left visual field.

Table 2.12 Seven cortical areas involved in saccades: afferents, efferents, functions.

Eye field	Afferents	Efferents	Functions/comments
DLPFC	Visual association cortex	SC, ipsilateral FEF, SEF, CCx	Voluntary saccades, approach and withdraw decisions
CCx	DLPFC, FEF, SEF	SC, ipsilateral FEF	Emotional significance of object; paying attention
SEF	DLPFC, PEF, Area 22	SC, ipsilateral FEF	Motor planning, multiple saccades
FEF	DLPFC, opposite FEF, PEF	SC, opposite PPRF, ipsilateral CCx	Voluntary saccades
Area 22	Auditory association area, PEF	Ipsilateral SC, neck movement	Saccades to sound source
PEF	'Where' pathway, pulvinar, DLPFC	Ipsilateral FEF, SC	Reflex (responsive) saccades
OC	Visual pathway	All cortical eye fields and SC	Interpretion and visual pursuit

CCx, cingulate cortex; DLPFC, dorso-lateral prefrontal cortex; FEF, frontal eye field; OC, occipital cortex; PEF, parietal eye field; PPRF, paramedian pontine reticular formation; SC, superior colliculus; SEF, supplementary eye field.

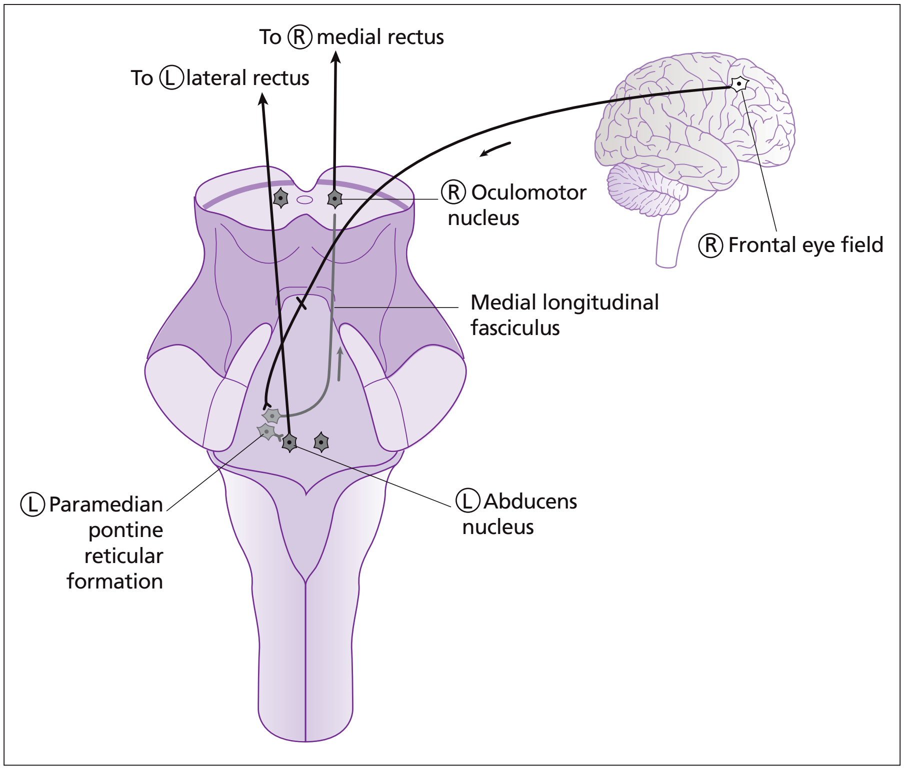

To Ⓡ medial rectus
To Ⓛ lateral rectus
Ⓡ Oculomotor nucleus
Ⓡ Frontal eye field
Medial longitudinal fasciculus
Ⓛ Paramedian pontine reticular formation
Ⓛ Abducens nucleus

Figure 2.43 Midbrain: posterior view: voluntary conjugate eye movement →left.

vestibular system. This explains some automatic movements, e.g. hands being in position to catch a rapidly moving ball before it becomes visible.

Eye and pupil movement below the level of the cortical eye fields consists of:

- Conjugate gaze mechanisms within the brainstem;
- Pupillary light reflexes;
- Individual cranial nerves III, IV and VI and the muscles supplied;
- Near and far responses.

Gaze centres in the brainstem

Horizontal (lateral) gaze centres lie in the right and left PPRF adjacent to each abducens nucleus. Upward gaze is controlled by the rostral interstitial nucleus (RiN) close to the pretectal nucleus (IIIrd nucleus level). This lies at the rostral end of the medial longitudinal fasciculus (MLF). This bundle connects each PPRF and abducens nucleus with the portion of the IIIrd nucleus that supplies the medial rectus – thus yoking together abduction in one eye with adduction in the other. The downward gaze centre is ventral to the RiN at the same level (Figure 2.43).

Pupillary light reflex

The pathway from retinal ganglion cell to post-ganglionic parasympathetic fibres and onwards to the iris (sphincter pupillae) is shown in Figure 2.44.

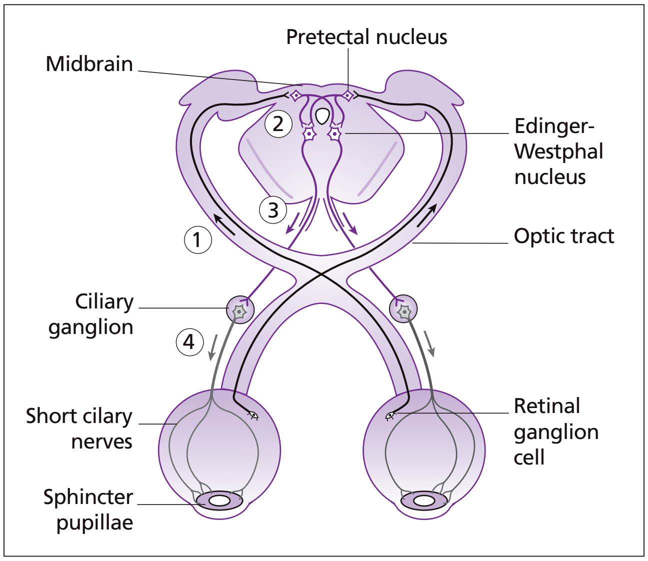

Pretectal nucleus
Midbrain
Edinger-Westphal nucleus
Optic tract
Ciliary ganglion
Short cilary nerves
Sphincter pupillae
Retinal ganglion cell
①
②
③
④

Figure 2.44 Pupillary light reflex pathway:
1 Retinal ganglion cell via optic tract – synapse at pretectal nuclei
2 Interneurones to both Edinger–Westphal parasympathetic nuclei (components of oculomotor IIIrd nerve nuclei)
3 Parasympathetic (preganglionic) fibres travel within III to synapse in the ciliary ganglion
4 Fibres (post-ganglionic) run within short ciliary nerves to terminate on sphincter pupillae.

III, IV and VI: third, fourth and sixth nerve nuclei and nerves

Some essential anatomy is summarized here (Figure 2.45). The features and relevance of lesions of these nerves and their nuclei are discussed in Chapters 3, 13, 14 and 19.

Oculomotor nucleus and IIIrd nerve

This compound nucleus, adjacent to the peri-aqueductal grey matter at superior colliculus level consists of neuronal cell bodies that supply:

- Five striated muscles: medial, superior, inferior recti, inferior oblique and levator palpbebrae superioris;
- Muscles supplied by the parasympathetic system: ciliaris (ciliary muscle) and sphincter pupillae, via the Edinger–Westphal nucleus.

The oculomotor (III) nerve passes through the midbrain tegmentum, emerges into the interpeduncular fossa, crosses the apex of the petrous temporal bone, enters the cavernous sinus and leaves in two divisions within the superior orbital fissure. Parasympathetic fibres travel in the lower division and leave in the branch to the inferior oblique muscle. They synapse in the ciliary ganglion, pierce the sclera and, via the short ciliary nerves, reach ciliaris and sphincter pupillae.

Trochlear nucleus and IVth nerve

The nucleus is at the level of the inferior colliculus. Each IVth nerve then decussates, emerges from the back of the brainstem, passes around it and enters the cavernous sinus (just below III). The nerve passes through the superior orbital fissure to supply the superior oblique muscle.

Abducens nucleus and VIth nerve

Each VI nucleus, lower in the brainstem than III and IV, lies in the mid pons at the level of the facial nucleus. The nerve runs a long intracranial course, initially beside the basilar artery, thence

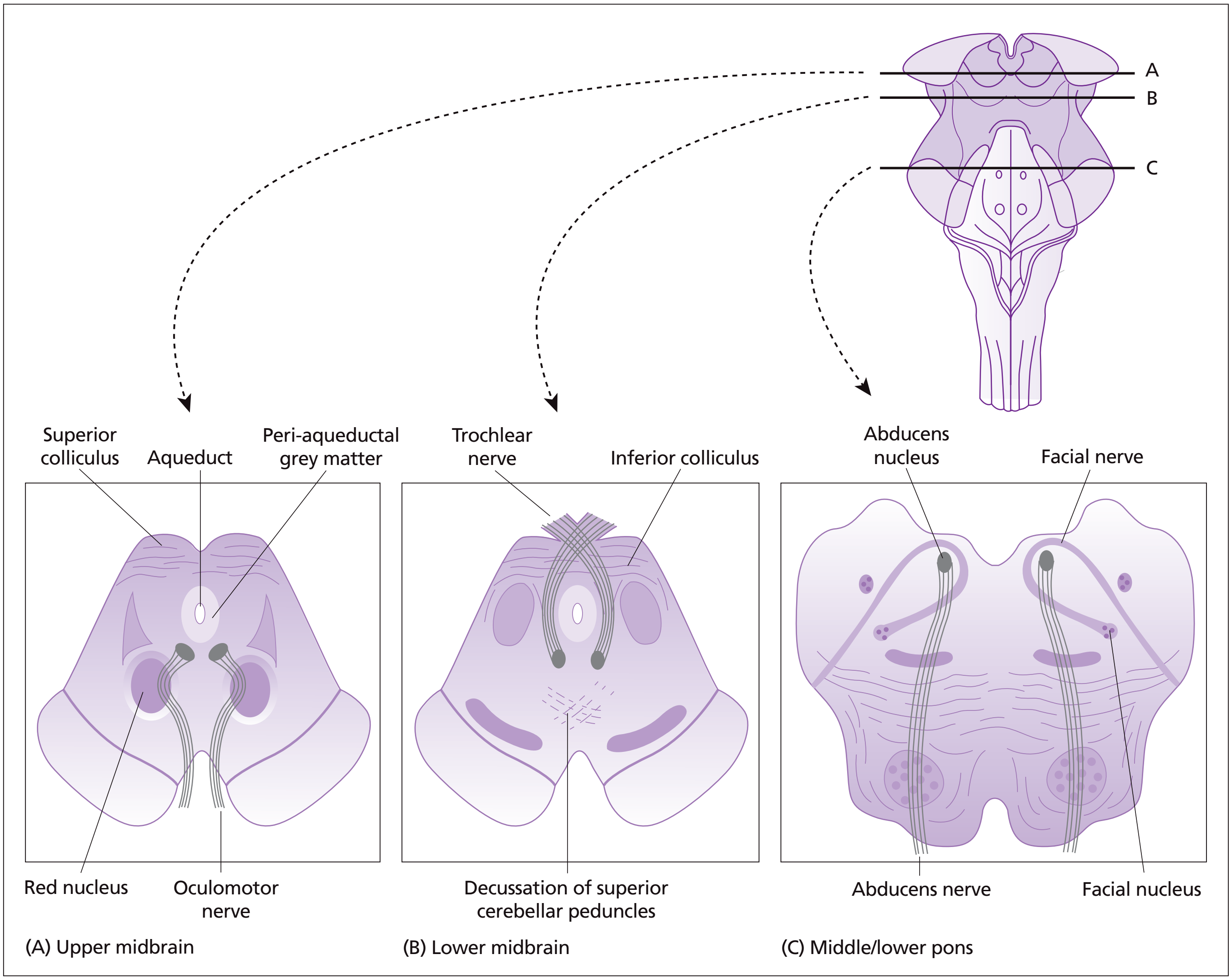

A
B
C
Superior colliculus
Aqueduct
Peri-aqueductal grey matter
Trochlear nerve
Inferior colliculus
Abducens nucleus
Facial nerve
Red nucleus
Oculomotor nerve
Decussation of superior cerebellar peduncles
Abducens nerve
Facial nucleus
(A) Upper midbrain
(B) Lower midbrain
(C) Middle/lower pons

Figure 2.45 Origins of III, IV and VI: transverse sections of brainstem.

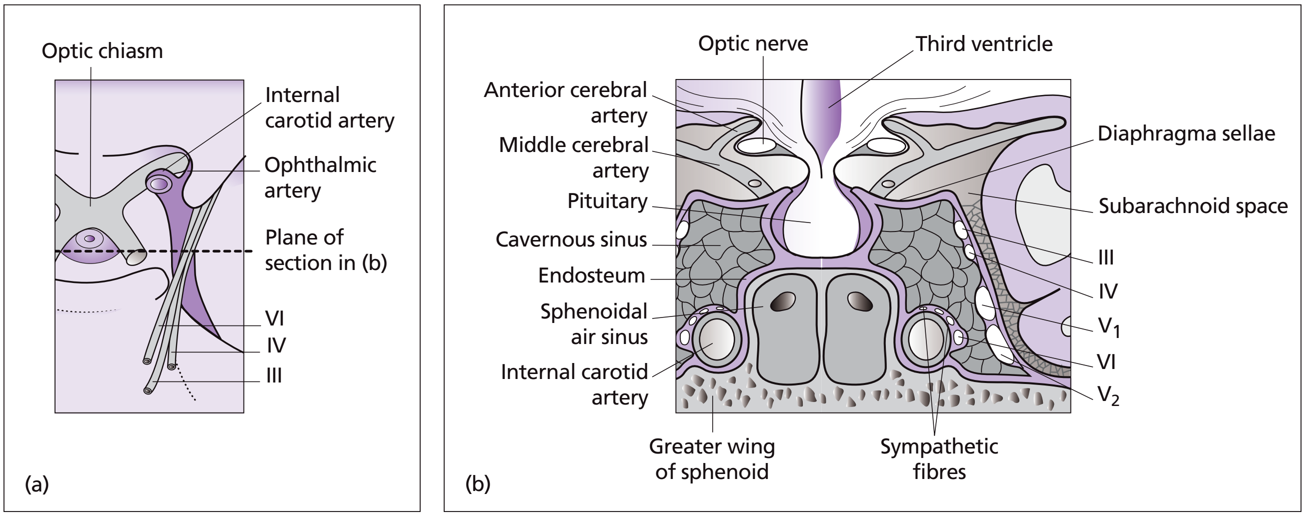

Optic chiasm
Internal carotid artery
Ophthalmic artery
Plane of section in (b)
VI
IV
III
(a)
Optic nerve
Third ventricle
Anterior cerebral artery
Middle cerebral artery
Pituitary
Cavernous sinus
Endosteum
Sphenoidal air sinus
Internal carotid artery
Diaphragma sellae
Subarachnoid space
III
IV
V1
VI
V2
Greater wing of sphenoid
Sympathetic fibres
(b)

Figure 2.46 Relations of III, IV, VI, V_1 and V_2 within cavernous sinus. (a) Right middle cranial fossa from above (cavernous sinus removed). (b) Coronal section through pituitary.

over the petrous temporal bone. Within the cavernous sinus it is applied to the internal carotid artery (Figure 2.46). Like III and IV, VI runs through the superior orbital fissure. VI innervates the lateral rectus muscle.

Motor units and sensory connections

These ocular muscle motor units contain 5–10 muscle fibres (cf. 500 or more in biceps and large striated limb muscles) and comprise A, B and C fibres:

- A fibres (fast twitch) are involved in saccades;
- B fibres (slow twitch) are used in smooth pursuit; and
- C fibres are involved in maintaining parallel visual axes and tonically active, when awake.

Proprioceptive pathways from the extraocular muscles extend widely – to the mesencephalic nucleus of V and to the cuneate nucleus in the medulla. Peripheral afferent projections from the neck muscles and output projections from the vestibulo-cerebellum to these nuclei assist coordinated simultaneous movements of the neck and head in response to changes in gaze.

The near response

Three responses combine to enable gaze to focus on a near object:

1 Covergence of the ocular axes is brought about by contraction of the medial recti;

2 The ciliary muscle contracts – the lens bulges passively, the thicker lens shortening its focal length (Figure 2.47); and

3 Sphincter pupillae contracts – concentrating light through the central part of the lens.

Retinal impulses pass via the lateral geniculate body to the occipital cortex, thence to the visual association cortex which analyses stereoscopically the object in view. Thence, the efferent pathway reaches the Edinger–Westphal nucleus and vergence cells within the reticular formation.

The far response

To bring a distant object into focus, the ciliary muscle must be inhibited – allowing the suspensory ligament to become tight and flatten the lens. Sympathetic impulses cause this relaxation of the ciliary muscle via β_2 receptors. This dilates the pupil (contraction of dilator pupillae) via α_1 receptors.

Sympathetic pathway to the eye and face

The sympathetic system originates in the hypothalamus. Central efferents decussate in the midbrain and are joined by ipsilateral fibres running within and from the reticular formation. The pathway descends in the cord, emerges in the first ventral thoracic root and reaches the sympathetic chain. These preganglionic fibres synapse in the superior cervical ganglion. Post-ganglionic fibres run within adventitia of branches of the internal and external carotid arteries. The internal carotid system is accompanied by two sets of fibres. One joins V_1 in the cavernous sinus, but leaves this nerve in the short and long ciliary nerves to the smooth muscles of the eye (dilator pupillae, ciliaris and tarsal muscle levator palpebrae superioris). The second forms a plexus around the internal carotid artery. Branches reach the skin of the forehead and scalp. (Horner's syndrome is discussed in Chapter 13.)

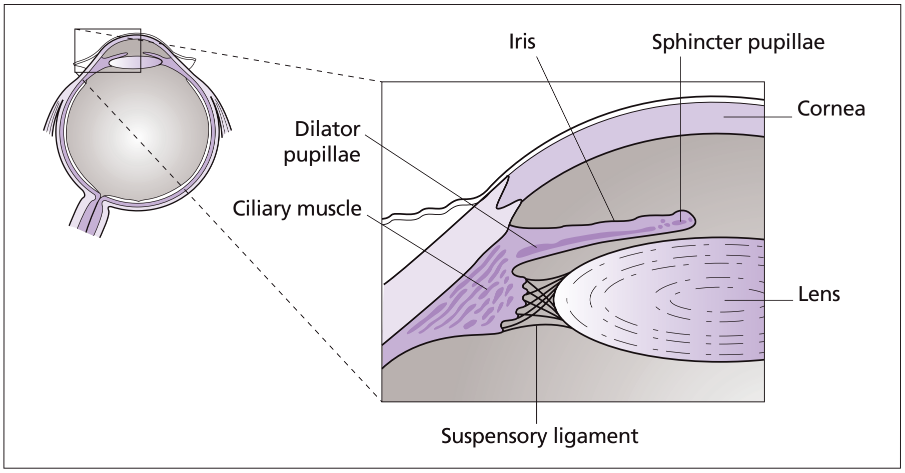


Figure 2.47 Dilator and sphincter pupillae, lens and ciliary muscle.

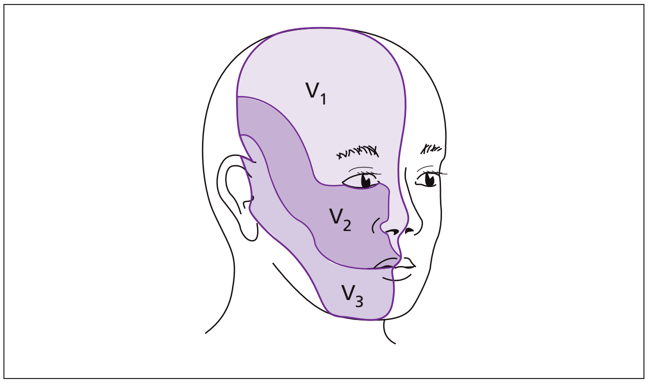


Figure 2.48 Cutaneous distribution of the three divisions of Vth nerve. (From Patten J. *Neurological Differential Diagnosis*, 2nd edn. London, New York, Springer, 1996, with permission.) Precise distribution varies amongst published sources.

External carotid sympathetic fibres are intimately related to all branches of the external carotid artery (e.g. superficial and middle temporal, facial, maxillary, middle meningeal, posterior auricular and lingual ateries).

V: trigeminal nerve and nuclei

The trigeminal nerve and its nuclei form a massive sensory input via the ophthalmic (V_1), maxillary (V_2) and mandibular (V_3) divisions. The sensory cutaneous distribution of the three divisions in Figure 2.48 will be familiar.

The Vth nerve carries sensation from:

- The eyes;
- Dura mater of anterior and middle cranial fossae;
- Adventitia of cerebral and basilar vessels;
- Paranasal sinuses;
- Teeth;
- Oral and nasal mucous membranes; and
- Facial and masticatory muscles.

A summary of the essential neuroanatomy follows.

Motor nucleus of V and supratrigeminal nuclei

Each Vth motor nucleus in the tegmentum of the pons supplies muscles of mandibular arch origin (Figure 2.49). Supranuclear connections run from each motor cortex to both these V motor nuclei, but largely to the contralateral. Within the reticular formation (see below) are the supratrigeminal nuclei, lying at the upper poles of the V motor nuclei. These generate masticatory rhythms. Muscles supplied via V_3 are:

- Temporalis;
- Masseter;
- Pterygoids and digastric;
- Infrahyoid muscles; and
- Tensor tympani and tensor palati.

Paralysis of one motor root causes deviation of the opening jaw to that side. The motor root is the efferent arc of the jaw jerk, a monosynaptic reflex.

Sensory Vth nuclei

There are three sensory Vth nerve nuclei (Figure 2.49):

1. Mesencephalic;
2. Principal (pontine); and
3. Spinal.

Mesencephalic Vth nucleus

Peripheral processes enter the sensory root via the trigeminal mesencephalic tract. The mesencephalic nuclear neurones are unique – they are cell bodies of primary sensory neurones. Their peripheral origins are the stretch receptors of masticatory muscle spindles (V_3) and stretch receptors of peri-odontal ligaments of the teeth (V_2, V_3) and some fibres from the eye and eye muscles (V_1). Central processes of the mesencephalic afferents descend through the tegmentum of the pons (tract of Probst). Most terminate in the supratrigeminal nucleus; others reach the main part of the motor nucleus, the pontine Vth nucleus and even the dorsal nucleus of the vagus (Figure 2.50).

Principal (pontine) Vth nucleus

These paired nuclei are homologues of the spinal gracile and cuneate nuclei. They process touch discrimination from the mouth, nose and face.

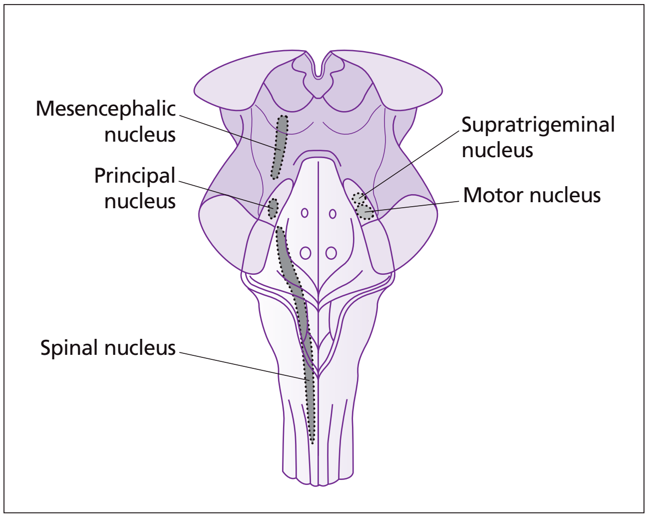

Mesencephalic nucleus
Principal nucleus
Spinal nucleus
Supratrigeminal nucleus
Motor nucleus

Figure 2.49 Trigeminal nuclei within the brainstem.

Spinal Vth nucleus

These paired nuclei extend from the pons to spinal level C3. Each main spinal Vth nucleus (pars caudalis) receives pain and temperature afferents from the entire trigeminal area and beyond.

Each nucleus is microscopically a continuation of the outer laminae (I–III) of the posterior horn of the cord. Pain modulation (see below) is similar to the situation in the cord (although exquisitely sensitive) – enkephalinergic and GABAergic connections in the substantia gelatinosa and serotoninergic fibres from the reticular formation (magnus raphe nucleus).

Each Vth spinal nucleus receives input from three principal sources:

1 Gasserian ganglion (trigeminal afferents);
2 IX and X; and the
3 Upper three cervical posterior roots (C1 is vestigial or absent).

Trigeminal afferents are the central processes of Gasserian ganglion neurones. Topographical representation within the nucleus is linear (mouth rostral) but layered, like an onion centred on the mouth (Figure 2.51). Peripheral fibres carry pain, temperature and touch centrally (facial skin, teeth, sinuses, cornea, temporomandibular joints, dura of anterior and middle fossae). Afferents from IX and X (middle ear, Eustachian tube, pharynx, larynx) also reach each inferior sensory ganglion of IX and X. Cervical

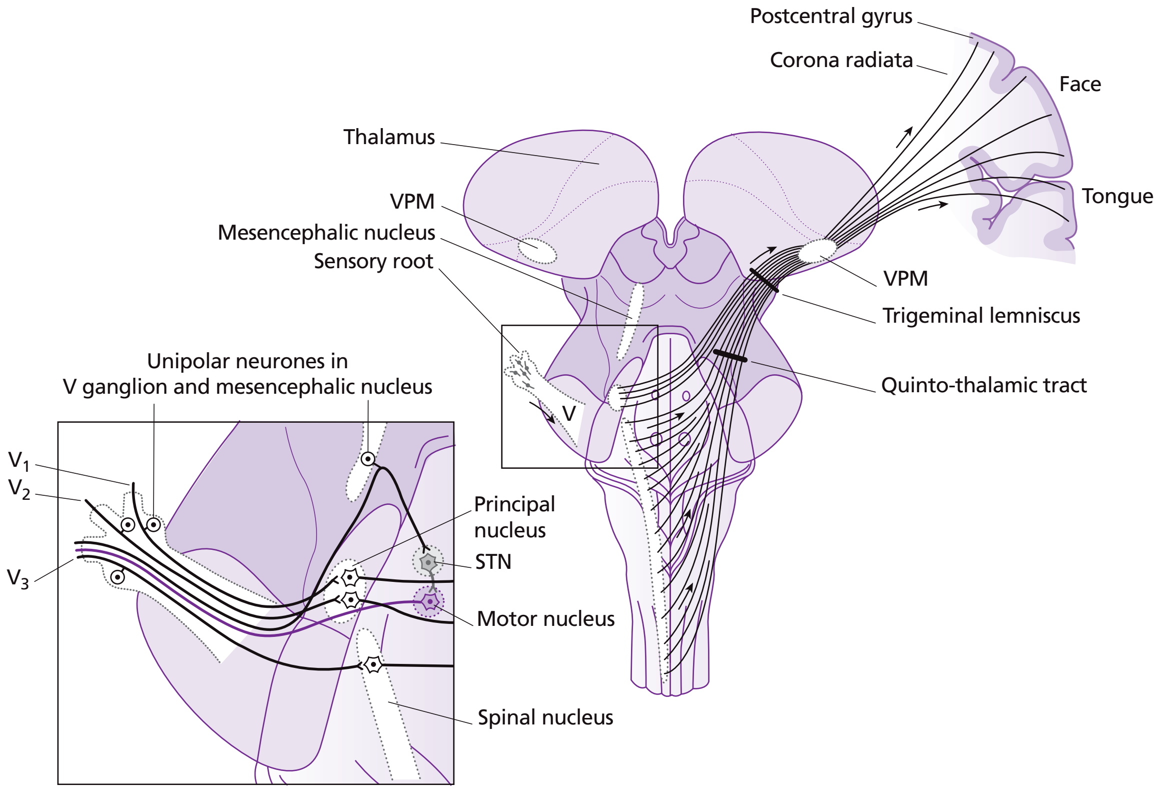

Postcentral gyrus
Corona radiata
Face
Tongue
Thalamus
VPM
Mesencephalic nucleus
Sensory root
VPM
Trigeminal lemniscus
Quinto-thalamic tract
V
Unipolar neurones in V ganglion and mesencephalic nucleus
V1
V2
V3
Principal nucleus
STN
Motor nucleus
Spinal nucleus

Figure 2.50 Trigeminal pathways within the brainstem. STN, supratrigeminal nucleus; VPM, ventral posterior medial nucleus of the thalamus.

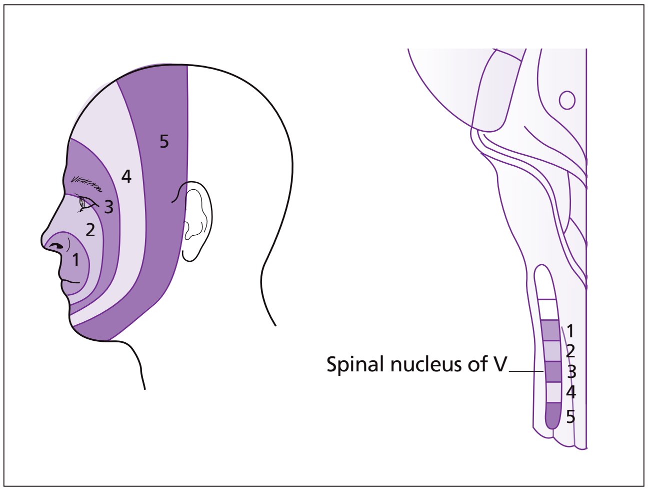


Figure 2.51 Spinal Vth nucleus and its facial distribution.

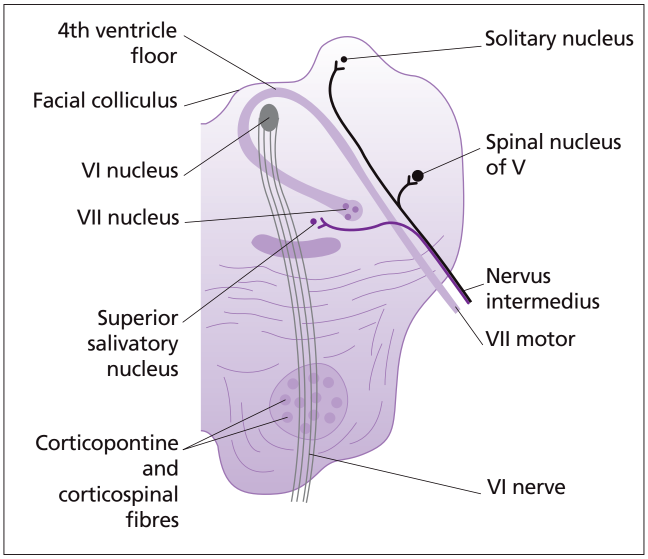


Figure 2.52 Pons: facial nucleus, facial and abducens nerves.

afferents (dura of posterior fossa and cord, cervical joints) ascend through the hypoglossal canal.

Trigemino-vascular system – innervation of cerebral vessels

V$_1$ lies close to the internal carotid artery in the cavernous sinus. Afferent V$_1$ fibres and autonomic fibres accompany the carotid artery, follow its branches and form a network throughout the intracranial vasculature. The role of this important system in the pathogenesis of headache is discussed in Chapter 11.

Trigemino-thalamic tract, lemniscus, cortical projection and reticular formation

The spinal Vth nucleus gives rise to the lower part of the trigemino-thalamic tract. This crosses the midline, ascends in the pons and carries pain, temperature and touch. Within the pons the tract is joined by fibres from the principal (pontine) Vth nucleus to form the trigeminal lemniscus – the ribbon of trigeminal fibres that terminates in the ventral posterior medial nucleus of the thalamus (Figure 2.50). Thence, third order afferents pass from the thalamus to the substantial facial area of the somatic sensory cortex.

Trigemino-reticular fibres synapse in the lateral RF (parvocellular neurones). They mediate the effect of slapping or irritating the face (arousal).

The jaw jerk and other masticatory reflexes

Spindle afferents from jaw muscles make direct synaptic contact with Vth motor nuclear neurones. Supranuclear lesions of the Vth motor nucleus (see Pseudo-bulbar palsy, Chapter 12) are accompanied by an exaggerated jaw jerk. This is a monosynaptic stretch reflex.

Other masticatory muscle reflexes (jaw closing in response to food in the mouth, and jaw opening – inhibition of jaw closure, chewing, snapping) are mediated via the pattern-generating supratrigeminal motor nuclei. They are of little diagnostic significance, but explain the potential hazard of being bitten by stuporose patients (or sleepy animals).

The corneal reflex

The afferent pathway is largely via pain fibres in the naso-ciliary branch of V$_1$. The efferent pathway is via VIIth nerve innervated muscles – bilateral blinking (Chapters 3, 12 and 19). While this is so, the clinical reality in an out-patient clinic is first that the patient feels (and reports) the unpleasant stimulus. Secondly, there is visible lacrimation and conjunctival injection in a normal eye, but these visible features diminish when there is a Vth nerve lesion. The upper five-sixths (or so) of the cornea is innervated by the ophthalmic division (V$_1$), while the lower sixth sector (from about 5 to 7 o'clock) by the maxillary division (V$_2$). Depression of the corneal reflex is the first sign of a Vth nerve lesion – a matter of signal importance in the early diagnosis of cerebello-pontine angle lesions in the era before non-invasive imaging.

VII: facial nerve

The facial nerve arises from the VIIth nucleus in the pons and before leaving the brainstem loops around the abducens (VI) nucleus (as the internal genu), creating the facial colliculus in the fourth ventricle floor (Figures 2.52 and 2.53). The nerve leaves the skull via the stylomastoid foramen (its only constituent). Principal motor branches supply muscles of facial expression. A small motor branch supplies the stapedius. VII also carries sensory taste fibres from the anterior two-thirds of the tongue via the chorda tympani.

Supranuclear connections allow the facial muscles to respond both in volitional and emotional activities, and bilaterally in many common habitual situations – smiling, blinking, frowning

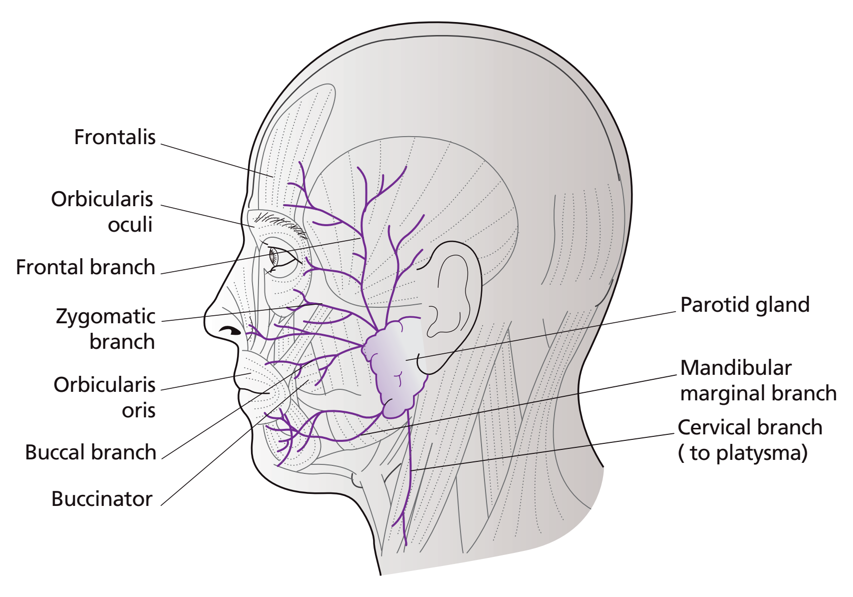


Figure 2.53 Principal facial branches of VIIth nerve.

Table 2.13 Reflexes involving V, VII, VIII and II.

	Corneal reflex	Jaw jerk	Pout reflex	Blink (light)	Blink (noise)	Stapedius
Receptor	Cornea	Masseter (spindles)	Lips	Retina	Cochlea	Cochlea
Afferent	V_1	V_3	V_2, V_3	Optic nerve	Cochlear nucleus	Cochlear nerve
1st synapse	V spinal nucleus	V motor nuclei	V principal nucleus	Superior colliculus	Inferior colliculus	Cochlear nucleus
2nd synapse	VII nucleus (+ pain & lacrimation V)	(Monosynaptic reflex)	VII nucleus	VII nucleus	VII nucleus	VII nucleus
Muscle	Orbicularis oculi	Masseter	Orbicularis oris	Orbicularis oculi	Orbicularis oculi	Stapedius (see Chapter 14)

– and in several reflex actions (Table 2.13). Part of each VIIth nucleus supplying the upper face (principally frontalis) receives supranuclear fibres from each hemisphere. The face muscles are exquisitely responsive to emotional states, and to all sensory input; the limbic contribution is from the nucleus accumbens in the ventral basal ganglia.

Nervus intermedius, greater petrosal nerve and chorda tympani

Distal to the internal genu, the nervus intermedius (part of VII) acts as one stage of a complex conduit (i.e. both to and fro) for parasympathetic and special sense fibres (Figure 2.54):

- The parasympathetic root arises from the superior salivatory nucleus to form motor components of the greater petrosal nerve (→ pterygopalatine ganglion → lacrimal and nasal glands) and the chorda tympani (→ submandibular ganglion → submandibular and sublingual glands).
- The special sensory root consists of cell bodies that lie in the geniculate ganglion. Afferent fibres from taste buds in the anterior two-thirds of tongue travel in the chorda tympani. Those from taste buds in the hard palate travel in the greater petrosal nerve. Central processes enter the gustatory nucleus, part of the nucleus solitarius that also receives fibres from IX. Thence, second order neurones project via the thalamus, to anterior insular and cingulate cortex.
- Some geniculate ganglion cells also receive sensory impulses from skin around external auditory meatus (see Bell's palsy, Chapter 12).

VIII: vestibulo-cochlear nerve

The vestibulo-cochlear nerve contains primarily afferent axons of bipolar neurones whose cell bodies lie within the petrous temporal bone. Peripheral processes of these neurones are in contact with specialized neuro-epithelium of the labyrinth and cochlea. The two components of VIII (vestibular and cochlear) enter the junction between pons and medulla at the cerebello-pontine angle.

The neuro-otological system is complex – an entire subspecialty is devoted to it (Chapter 14). Vertigo – the illusion of

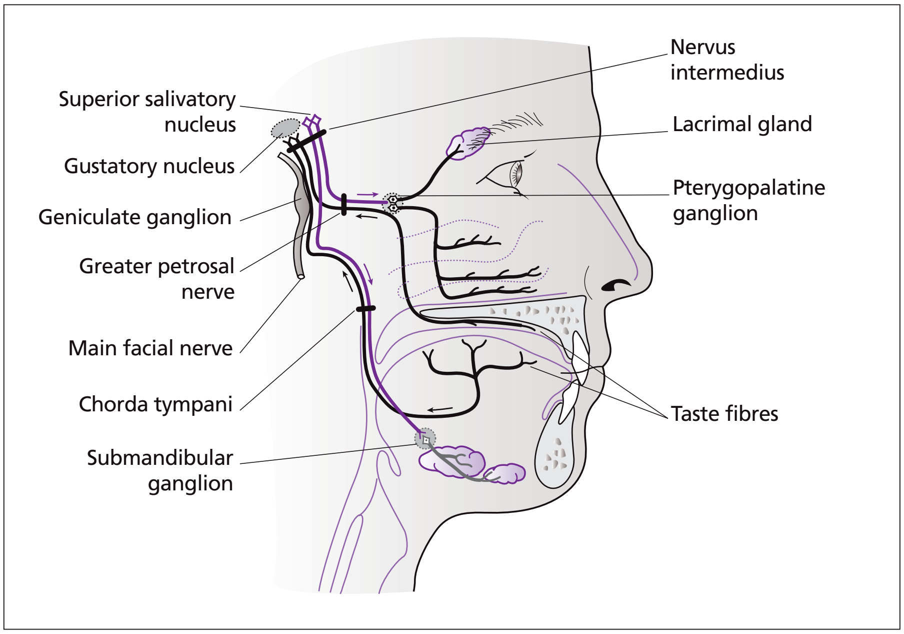


Figure 2.54 Nervus intermedius and its connections.

movement, with hearing loss and tinnitus – are the prominent symptoms. The purpose here is to outline the essential peripheral neuroanatomy and summarize the central connections (Figure 2.55).

Vestibular system

The dense petrous temporal bony labyrinth contains perilymph (like extracellular fluid) that provides a fluid housing for the membranous labyrinth that encloses the organs of balance. These are washed by endolymph: K^+ rich, Na^+ poor – similar to intracellular fluid.

Each labyrinth (Figure 2.55a) houses five sensory organs within the utricle, saccule and three semi-circular canals (or ducts). Each utricle and each saccule contains a macula. Each canal contains a crista within an ampulla:

- Maculae (two) are sensory organs of static head position;
- Cristae (three) are sensory organs of head movement.

The vestibular ganglion lies in the internal auditory meatus. Peripheral processes are applied to the five sensory organs. Central axons (i.e. vestibular nerve) enter the brainstem to synapse at the lateral, medial, superior and inferior vestibular nuclei (VN). Other connections are shown in Figure 2.55d.

The static labyrinth

In the erect posture:

- The utricular macula is essentially horizontal;
- The saccular macula is essentially vertical.

Hair cells in these maculae are in contact with vestibular nerve fibres via ribbon synapses (Figure 2.55b). Stereocilia (about 100/cell) and a longer process, a kinocilium (one/cell) projects into otoconia (ear sand) – a gelatinous matrix of calcium carbonate crystals. Each macula has a central groove, a striola. Cilia are arranged either side of each striola, as in a mirror. Depolarization takes place whenever kinocilia are parted from stereocilia.

The maculae respond to:

- Linear acceleration (e.g. walking);
- Vertical acceleration (e.g. falling); and
- Tilting.

The roles of the static labyrinth are to indicate head position in relation to the trunk, and to alter centre of gravity of the body and maintain upright (or other posture). The system is adapted to work within, and to compensate for the Earth's gravitational field.

The kinetic labyrinth

In the kinetic labyrinth, the ciliated, cellular arrangement of the static labyrinth is replicated in the cristae of the three semicircular canals, their ampullae and each cupula (Figure 2.55c). The cupula is a gelatinous projecting part of each crista within an ampulla – bathed in endolymph. Into each cupula, kinocilia project from hair cells.

The three cupulae are quite exquisitely sensitive to angular acceleration and deceleration. Endolymph remains relatively static. Each crista billows and deflects as this miniature sail-like organ is thrust against endolymph as head velocity changes in a particular plane.

Vestibular nuclei and central connections

Central axons of each vestibular nerve synapse at the lateral, medial, superior and inferior vestibular nuclei (VN) in the brainstem (Figure 2.55d).

The lateral vestibulo-spinal tract arises from the lateral VN (nucleus of Dieter). Fibres descend in the anterior funiculus of the cord to synapse with a complex variety of limb, neck and

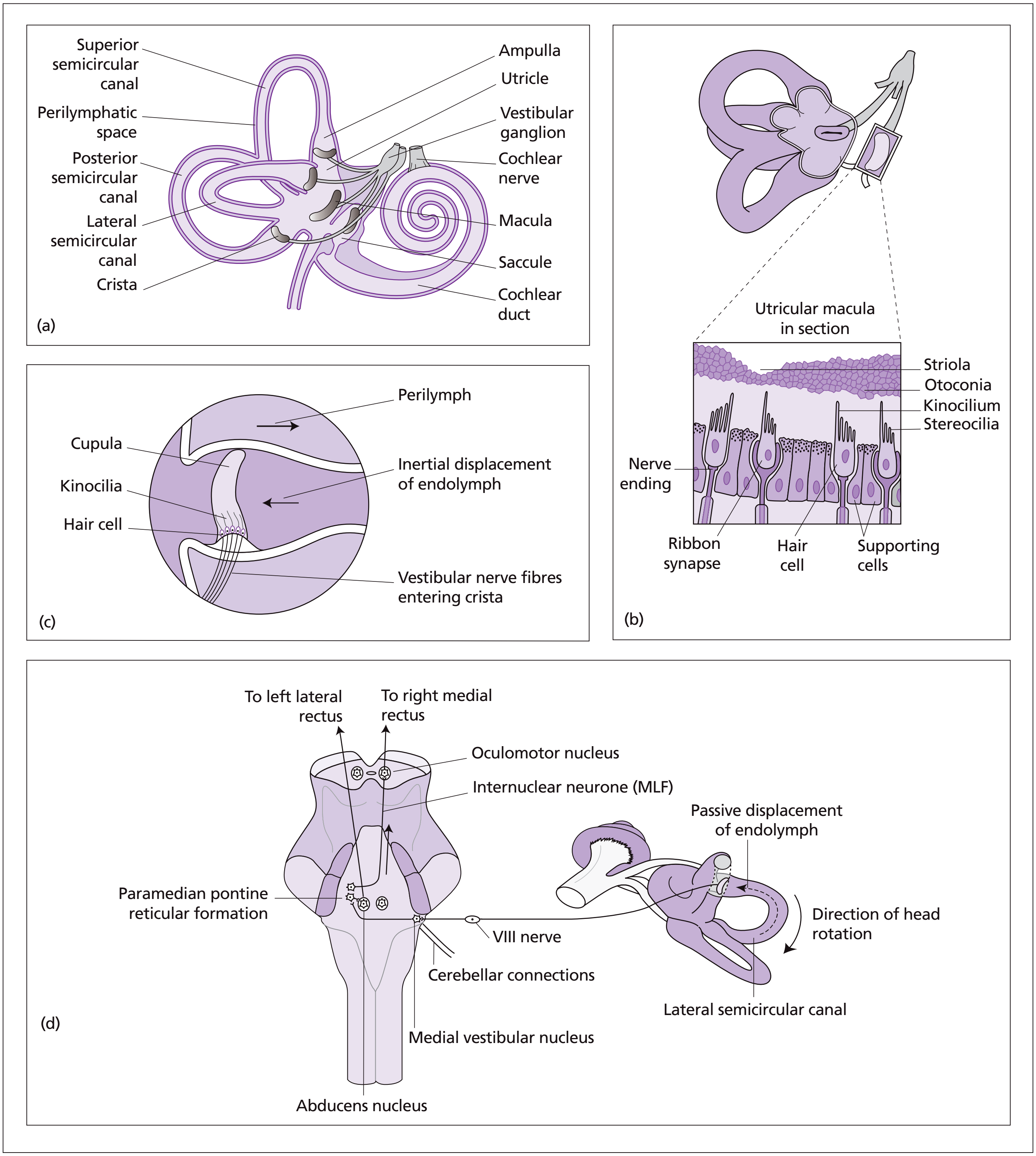

Superior semicircular canal
Perilymphatic space
Posterior semicircular canal
Lateral semicircular canal
Crista
Ampulla
Utricle
Vestibular ganglion
Cochlear nerve
Macula
Saccule
Cochlear duct
(a)
Utricular macula in section
Striola
Otoconia
Kinocilium
Stereocilia
Nerve ending
Ribbon synapse
Hair cell
Supporting cells
(b)
Perilymph
Cupula
Kinocilia
Hair cell
Inertial displacement of endolymph
Vestibular nerve fibres entering crista
(c)
To left lateral rectus
To right medial rectus
Oculomotor nucleus
Internuclear neurone (MLF)
Passive displacement of endolymph
Paramedian pontine reticular formation
Direction of head rotation
VIII nerve
Cerebellar connections
Lateral semicircular canal
Medial vestibular nucleus
Abducens nucleus
(d)

Figure 2.55 (a) Vestibulo-cochlear sytem and five vestibular sense organs. (b) Cells of static labyrinth. (c) Crista in ampulla of semi-circular canal. (d) Central connections, e.g. head rotation. MLF, medial longitudinal fasciculus.

trunk α and γ motor neurones concerned with posture. The flocculo-nodular lobe of the cerebellum has two-way connections with all vestibular nuclei.

The medial vestibulo-spinal tract arises in the inferior and medial VN, descends in the medial longitudinal fasciculus and ends in the cervical cord. Head and eye-righting reflexes are dealt with by this system; there are connections with the kinetic labyrinth.

Central second order neurones from the VN reach the contralateral VP nucleus of the thalamus. Third order neurones project to the various cortical areas – close to the facial area in the somatosensory cortex, to the insula and temporoparietal cortex. For vertigo, mystery surrounds the location of a cortical area specifically associated with this symptom, although electrical stimulation of somato-sensory cortex sometimes induces it. Vertigo is a relative rarity as an epileptic event – but vertigo does occur with focal seizure activity in the temporoparietal cortex.

One relevant feature of the vestibular system – and a reason why vertigo, nystagmus (and dizziness) have relatively poor localizing value – is that right–left imbalance in the system, at any level, produces symptoms and/or signs. (Nystagmus is discussed in Chapters 3 and 14.)

Auditory system

Normal binaural hearing is complex (Chapter 14). Sound quantity, quality, position, timing and relevance are detected via:

- Cochlea and cochlear nerve;
- Cochlear nuclei and central pathways; and
- Auditory cortex.

Secondary projections, that interpret the emotional content of sound, and music – and determine actions in response to sounds.

The afferent system is illustrated in Figure 2.56. Auditory efferents are mentioned in Chapter 14.

Cochlea

Hair cells, from which protrude stereocilia, form the principal auditory neuro-epithelium. They lie within the organ of Corti (spiral organ). The complex terminology is summarized below:

- The modiolus is the central bony pillar of the cochlea – it is in the line of the internal auditory meatus.
- The osseous spiral lamina projects from the modiolus. The cochlear spiral has two and half turns and is about 1 cm both in height and diameter.
- The basilar membrane is fixed to the tip of the spiral lamina. It extends across the cavity of the bony cochlea and is attached to the spiral ligament.
- The scala vestibuli and the scala tympani are the upper and lower chambers of the cochlea. They are filled with perilymph. They communicate via the helicotrema.
- The scala media lies above the basilar membrane and is filled with endolymph – and separated from the scala vestibuli by the vestibular membrane.
- The organ of Corti (spiral organ) lies on the basilar membrane. The organ contains a central tunnel (tunnel of Corti) containing perilymph diffusing through the basilar membrane.

The arrangement of inner and outer hair cells, tectorial membrane and ribbon synapses is shown in Figure 2.56. Their nerve supply (the cochlear nerve) is via bipolar spiral ganglion cells in the osseous spiral lamina. One inner hair cell has some 20 afferent fibres in contact with it.

Auditory transduction

The snug fit and sensitive articulation of the ossicles – 'the footplate of the stapes rests on the oval window' – transmits vibration, i.e. pressure waves through the tympanic membrane to the basilar membrane. The basilar membrane is tonotopic:

- Low frequency waves produce resonance where the fibres are longest – at the apical turn of the cochlea;
- High frequency waves (high-pitched sounds) cause short fibres in the basal part of the cochlea to resonate.

Cochlear nerve and central connections

Myelinated axons from some 25,000 large bipolar neurones form the cochlear nerve. The pathways are illustrated in Figure 2.56. The sequence is:

- Inferior and superior cochlear nuclei (termination of first order fibres);
- Trapezoid body (second order fibres), superior olivary nucleus to inferior colliculus;
- Inferior brachium via medial geniculate body to auditory cortex.

The primary auditory cortex is located in Heschl's gyrus on the anterior surface of the temporal lobe. In humans, destruction of this region on one side causes no perceptible deafness but an initial inability to localize sound. Hearing loss is produced rarely by central lesions – potential imbalance is compensated by bilateral representation. The usual focus of clinical neurology is the distinction between conductive and sensorineural deafness (Chapters 3 and 14).

Acoustic reflex pathways

Biologically important auditory automatic pathways include:

- Startle and waking responses, via the reticular formation.
- Dampening of sounds, e.g. the sound of one's own voice via tensor tympani (V) and the stapedius reflex (Chapter 14). The stapedius reflex consists of a contraction of stapedius muscle in response to loud noise. Hyperacusis occurs when the muscle is paralysed, e.g. in Bell's palsy (Chapter 12).
- Head turning and eye turning in response to sounds.
- Pleasurable experience, e.g. of music and rhythm.
- Automatic responses to the call (or command) of a dominant mate or pack leader.

IX, X, XI and XII: glossopharyngeal, vagus, accessory and hypoglossal nerves

These four cranial nerves are grouped together. These notes indicate their intricacy, multiple nuclei and complex pathways both

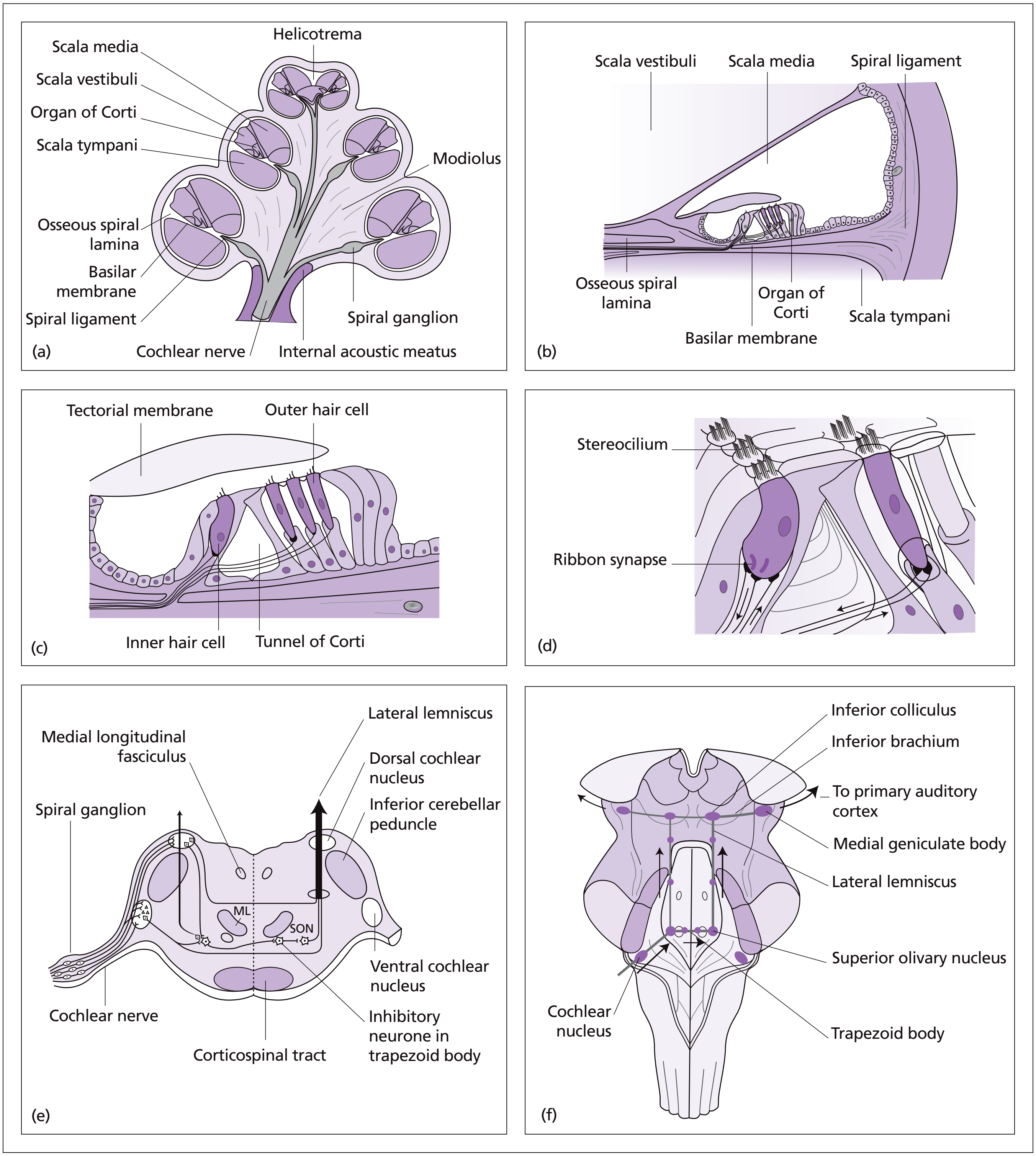

Helicotrema
Scala media
Scala vestibuli
Organ of Corti
Scala tympani
Modiolus
Osseous spiral lamina
Basilar membrane
Spiral ligament
Spiral ganglion
Cochlear nerve
Internal acoustic meatus
(a)
Scala vestibuli
Scala media
Spiral ligament
Osseous spiral lamina
Organ of Corti
Scala tympani
Basilar membrane
(b)
Tectorial membrane
Outer hair cell
Inner hair cell
Tunnel of Corti
(c)
Stereocilium
Ribbon synapse
(d)
Lateral lemniscus
Medial longitudinal fasciculus
Dorsal cochlear nucleus
Inferior cerebellar peduncle
Spiral ganglion
ML
SON
Ventral cochlear nucleus
Cochlear nerve
Inhibitory neurone in trapezoid body
Corticospinal tract
(e)
Inferior colliculus
Inferior brachium
To primary auditory cortex
Medial geniculate body
Lateral lemniscus
Superior olivary nucleus
Cochlear nucleus
Trapezoid body
(f)

Figure 2.56 Outline anatomy of auditory system. ML, medial lemniscus; SON, superior olivary nucleus.

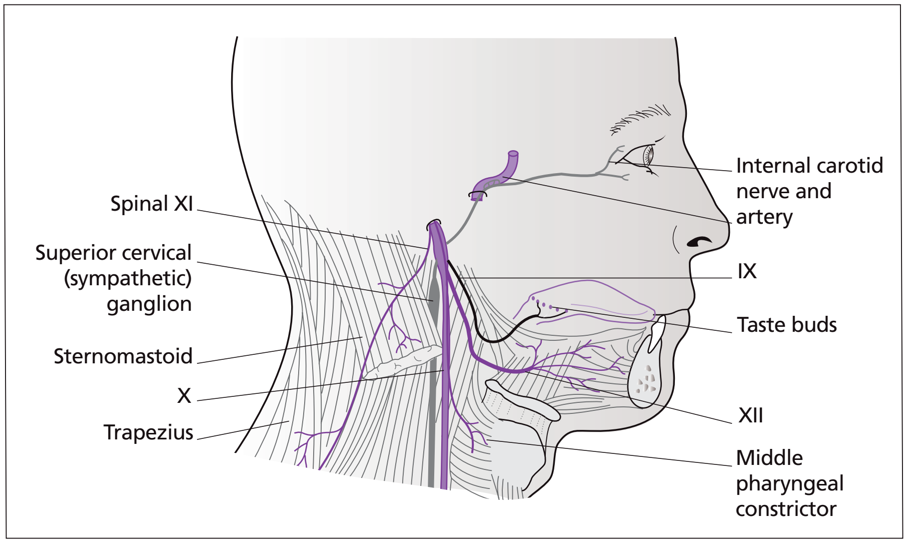

Spinal XI
Superior cervical (sympathetic) ganglion
Sternomastoid
X
Trapezius
Internal carotid nerve and artery
IX
Taste buds
XII
Middle pharyngeal constrictor

Figure 2.57 Distribution of IX, X, XI, XII & superior cervical ganglion.

afferent and efferent. Their distribution is shown in Figure 2.57 and the complex nuclear arrangement in Figure 2.58.

XI: spinal accessory nerve

The spinal accessory (XI) is the motor nerve to extrafusal and intrafusal fibres of trapezius and sternomastoid. The nuclear column (α and γ motor neurones) is in the anterior grey horn (lateral column) of the upper five segments of the cord, from which rootlets emerge (Figure 2.58b). The curious route of this nerve is upwards through the foramen magnum, then back, down and out through the jugular foramen. Some afferent twigs (cervical and thoracic nerves) combine with spinal XI as it pierces the trapezius, giving rise to a situation believed to be unique for the nerve supply of a muscle: muscle efferents (spinal XI) and muscle afferents (cervical and thoracic twigs) travel by separate pathways. This anatomical anomaly may be implicated in the extreme pain that follows section of motor roots of XI, or spinal XI in the neck.

In the posterior triangle of the neck, spinal XI is distinctly vulnerable (Chapter 12) – and readily damaged at biopsy of lymph nodes in this region.

Cranial accessory XI, glossopharyngeal IX and vagus X – and their nuclei

Groups of medullary neurones known as the nucleus ambiguus and the solitary nucleus contain some of the cell bodies of nerves IX, X and cranial XI.

The nucleus ambiguus (Figure 2.58b) provides special visceral efferent fibres of IX and cranial XI supplying:

- Pharynx (constrictor muscles);
- Stylopharyngeus and levator palati;
- Larynx (intrinsic muscles); and
- Oesophagus (striated muscles of the upper third, via the recurrent laryngeal nerve).

The solitary nucleus (Figure 2.58a,f) merges with its opposite number to form the commissural nucleus. The four functional regions of the solitary nucleus are:

1. Gustatory – afferents from tongue, epiglottis and palate;
2. Dorsal respiratory;
3. Baroreceptor – afferents from carotid sinus and aortic arch; and
4. Visceral afferent – afferents from gut and respiratory tract.

The cranial (accessory) nerve XI arises from the nucleus ambiguus in the medulla and leaves the skull through the jugular foramen. This nerve simply shares a dural sheath with spinal XI, without exchanging fibres. Cranial XI becomes incorporated into the vagus.

Glossopharyngeal nerve IX

The IXth nerve, almost entirely sensory, leaves the skull via the jugular foramen to reach the mucous membrane of the pharynx and the ear. The tympanic branch of IX (this leaves above the jugular foramen) supplies the tympanic membrane. Some central processes synapse with the spinal Vth nucleus. Some of the tympanic branch fibres are parasympathetic – they supply the parotid gland via the lesser petrosal nerve and otic ganglion. The oropharynx and posterior third of the tongue (touch) are supplied by fibres passing to the commissural nucleus. These provide the afferent limb of the gag reflex. Taste fibres (gustatory neurones in the circumvallate papillae of the tongue) terminate centrally in the gustatory nucleus. The carotid branch of IX contains two sets of fibres. One arises in baroreceptor neurones of the carotid sinus and passes to the solitary nucleus. The second arises in glomus cells (chemoreceptors) within the carotid body that terminate centrally in the dorsal respiratory nucleus. Stylopharyngeus muscle is supplied by branchial efferents of IX from the nucleus ambiguus.

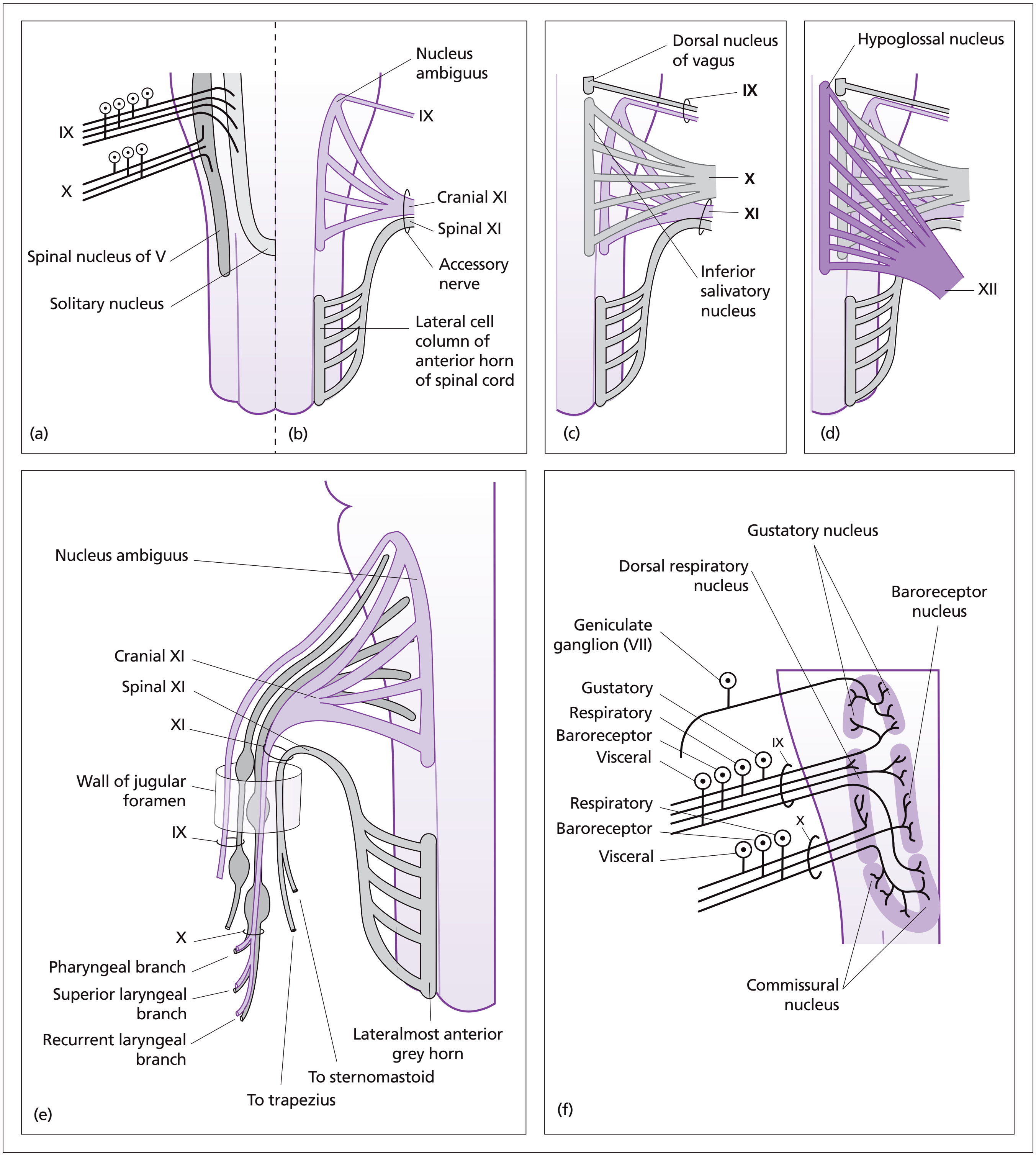

IX
X
Spinal nucleus of V
Solitary nucleus
(a)
Nucleus ambiguus
IX
Cranial XI
Spinal XI
Accessory nerve
Lateral cell column of anterior horn of spinal cord
(b)
Dorsal nucleus of vagus
IX
X
XI
Inferior salivatory nucleus
(c)
Hypoglossal nucleus
XII
(d)
Nucleus ambiguus
Cranial XI
Spinal XI
XI
Wall of jugular foramen
IX
X
Pharyngeal branch
Superior laryngeal branch
Recurrent laryngeal branch
To trapezius
To sternomastoid
Lateralmost anterior grey horn
(e)
Gustatory nucleus
Dorsal respiratory nucleus
Baroreceptor nucleus
Geniculate ganglion (VII)
Gustatory
Respiratory
Baroreceptor
Visceral
IX
Respiratory
Baroreceptor
Visceral
X
Commissural nucleus
(f)

Figure 2.58 Nuclear arrangements of IX, X, XI and XII. (a) to (d): anterior views of brainstem (a) Sensory nuclei. (b) Motor nuclei (special visceral efferent column) of IX, cranial XI and spinal XI. (c) Motor (general visceral efferent) column of IX and X. (d) Hypoglossal nucleus (somatic efferent column) giving rise to XII. (e) Nucleus ambiguus (special visceral afferent column): fibres to IX, X, cranial XI. (f) Solitary nucleus: four functional nuclear areas.

Vagus nerve X

The vagus (Latin = wandering) is both the largest visceral afferent and a major parasympathetic nerve. Some fibres arise from the dorsal nucleus of the vagus (Figure 2.58c) and others from the nucleus ambiguus. Some cell bodies (afferent fibres) lie within the solitary nucleus. Its rootlets in the medulla are in series with cranial XI and IX. It emerges from the skull in the jugular foramen with these two nerves. In the jugular foramen are the two small sensory ganglia of the vagus: the jugular and nodose ganglia.

A summary of branches of the vagus follows:

- Parasympathetic (efferent) neurones to the heart, lungs and gut originate from the dorsal nucleus of the vagus and nucleus ambiguus.
- General visceral afferent fibres from the heart, lungs and gut have cell bodies within the nodose ganglion. Central synapses are in the commissural nucleus. These pathways serve:
- The cough reflex;
- The Hering–Breuer reflex (inhibition of the dorsal respiratory centre by pulmonary stretch receptors);
- The Bainbridge reflex (increase in pulse rate following right atrial distension); and
- Gut afferents signalling satiety (to the hypothalamus).
- Special viscerent efferent neurones in the nucleus ambiguus supply pharyngeal and laryngeal muscles, levator palati and muscles (striated) of the upper third of the oesophagus.
- The auricular branch supplies skin of the external auditory canal. A meningeal branch supplies meninges of the posterior fossa. Both have cell bodies in the jugular ganglion. Central processes also pass to the spinal nucleus of V (Figure 2.58a).
- Chemoreceptors of the aortic bodies, baroreceptors of the aortic arch and taste buds of the epiglottis, are also supplied. The latter synapse in the gustatory nucleus.

XII: hypoglossal nerve

The motor nerve to the tongue originates from the XIIth nucleus lying in the fourth ventricular floor (in the same cell column as II, IV and VI; Figure 2.58d). Nerve rootlets leave the medulla between the pyramid and olive, form two fascicles and exit the skull via the anterior condylar foramen (hypoglossal canal), just below the jugular foramen. The nerve passes between the jugular vein and internal carotid artery at the skull base to reach the muscles of the tongue.

The hypoglossal nerve, like its fellow lower cranial nerves, has connections with others – it receives twigs from the vagus, from the upper cervical roots, from the cervical sympathetic (see Superior cervical ganglion) and has connexions with the lingual nerve. Styloglossus, hyoglossus, genioglossus and geniohyoid are the muscles supplied.

A unilateral XIIth nerve lesion is followed by deviation of the tongue to that side and several weeks later by wasting and fasciculation. (The surface of the normal tongue when protruded often flickers slightly.) Lateral tongue deviation is the obvious sign, although rarely a spontaneous complaint. The larynx is also drawn to the side opposite a hypoglossal palsy on swallowing (see also Chapters 3 and 12).

Autonomic nervous system

The autonomic (i.e. self-regulating) system is a diffuse neural network with these components:

- Controlling centres (hypothalamus and reticular formation) that connect to:
- Preganglionic neurones (grey matter of brainstem and cord) that project via:
- Preganglionic fibres that leave the CNS, to synapse at:
- Peripheral autonomic ganglia (multi-polar neurones), the origin of:
- Post-ganglionic fibres (unmyelinated) that form terminal networks on:
- Target tissues.

Division into sympathetic and parasympathetic retains much of its original value. Chapter 23 outlines issues of particular clinical relevance and includes schematic diagrams of the system.

Sympathetic system

The sympathetic outflow is thoraco-lumbar. Preganglionic neurones are located in the lateral grey horn at lower thoracic, L1, L2 and usually L3 levels. From these spinal neurones, preganglionic fibres leave the cord via corresponding anterior spinal nerve roots to form each paravertebral sympathetic chain.

Thereafter, preganglionic fibres reach sympathetic ganglia by four routes:

1. Some ascend. These synapse in cervical (superior, middle) and stellate ganglia.
2. Others descend. These synapse in lumbar and sacral sympathetic ganglia.
3. Some synapse locally (at a nearby ganglion). Post-ganglionic fibres within T1–L2 spinal nerves supply T1–L2 vessels, skin and sweat glands.
4. Some traverse the sympathetic chain, leave as lumbar/thoracic splanchnic nerves (preganglionic) and reach mesenteric, coeliac, renal and pelvic ganglia.

Sympathetic activity dilates the pupils, increases sweating, increases blood pressure and heart rate, diverts blood from skin and gut to skeletal muscle and closes sphincters.

Parasympathetic system

Parasympathetic preganglionic outflow is cranial and sacral. Fibres emerge via:

- IIIrd, VIIth, IXth and Xth cranial nerves;
- Sacral nerve roots.

Cranial parasympathetic III, VII, IX and X fibres and subsequent ganglia

Preganglionic fibres synapse at four cranial ganglia and one diverse ganglia system:

- Ciliary ganglion, via III to the pupil (see Constriction to light and near reflex);

- Pterigo-palatine ganglion, via VII to the lacrimal and nasal glands (secretion);
- Submandibular ganglion, also via VII to submandibular and sublingual glands;
- Otic ganglion, via IX to the parotid gland; and
- Mural and intramural ganglia, via X to the heart, lungs, oesophagus, pancreas, gallbladder, stomach, small and large bowel.

Sacral parasympathetic fibres and ganglia

From the cord lateral grey matter of S2, S3 and S4 (at L1 vertebral level within the conus), preganglionic fibres lie in the cauda equina within S2–4 ventral nerve roots. They leave the region via sacral vertebral foramina to emerge as pelvic splanchnic nerves. These synapse at:

- Pelvic ganglia (paired) that supply the detrusor muscle and tunica media of the internal pudendal vessels and cavernous tissue of the clitoris/penis; and
- Mural ganglion cells in the distal colon and rectum.

Neurotransmission within the autonomic system

A brief introduction follows. There is significant variation at local level: rules established for one target organ do not always hold for another.

Neurotransmission at sympathetic and parasympathetic ganglia

This is cholinergic throughout the system. The preganglionic neurons liberate ACh at axo-dendritic synapses. Ganglion cell receptors are nicotinic.

Neuro-effector junction transmission at target tissues

Neurotransmitters are secreted along terminal dendrites at target tissues, e.g. pupils, blood vessels, secretory glands. The chief neurotransmitter at sympathetic neuro-effector junctions is noradrenaline, i.e. post-ganglionic transmission is noradrenergic. An exception is the cholinergic sympathetic supply to eccrine sweat glands. The chief neurotransmitter at parasympathetic neuro-effector junctions is ACh, i.e. post-ganglionic transmission is cholinergic.

Junctional receptors at target tissues

Two factors influence the effect of physiological stimulation of target organs:

1 The nature of post-junctional receptors; and
2 The nature of pre-junctional receptors.

Sympathetic system receptors

For noradrenaline, two varieties of α-adrenoceptor and two varieties of β-adrenoceptor are known to exist:

- Post-junctional α_1-adrenoceptors. These initiate contraction of dilator pupillae, arteries and arterioles, sphincters and vas deferens.
- Pre-junctional α_2-adrenoceptors. These inhibit transmitter release at both sympathetic and parasympathetic terminals.
- Post-junctional β_1-adrenoceptors. In the heart these increase the force of ventricular contraction. In the kidney they increase renin secretion in response to a fall in blood pressure.
- β_2-Receptors respond to circulating and locally available noradrenaline. Post-junctional β_2-receptors relax smooth muscle (e.g. in bronchi, pupil). Pre-junctional β_2-receptors on adrenergic terminals promote noradrenaline release.

Parasympathetic junctional receptors

These are muscarinic in action. Stimulation:

- Slows the heart rate (vagal tone increases);
- Causes bladder emptying, pupillary accommodation for near vision, intestinal peristalsis; and
- Initiates glandular secretion, e.g. lacrimation.

Other autonomic neurotransmitter systems

The complexity of the autonomic system is compounded by at least three further neurotransmitter lineages, known as non-adrenergic non-cholinergic (NANC) neurones:

- Dopamine is liberated from small interneurones in sympathetic ganglia, exerting a mild inhibitory effect on adrenergic neurones.
- Nitric oxide is important in the parasympathetic system as a powerful arterial dilator.
- Vaso-active intestinal polypeptide (VIP) is known to be active as a neurotransmitter in salivary and sweat glands. It acts as a co-transmitter to ACh and is a vasodilator, increasing blood supply to a target organ already stimulated by muscarinic parasympathetic activity.

The relevance of this basic autonomic neuroanatomy and neurotransmitter data is discussed in Chapter 23 and in appropriate clinical sections.

Acknowledgement

Professor MJT FitzGerald, Emeritus Professor, Department of Anatomy, University College, Galway and the publishers kindly agreed that figures from the award-winning textbook *Clinical Neuroanatomy and Related Neuroscience* (FitzGerald MJT, Folan-Curran J, 4th edition, 2002; WB Saunders, Edinburgh) were made available for the authors to use in the preparation of this chapter; this has proved invaluable.

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3

The Language of Neurology: Symptoms, Signs and Basic Investigations

Charles Clarke, Richard Frackowiak, Robin Howard, Martin Rossor, Simon Shorvon

Introduction

Knowledge of neuroanatomy and basic neuroscience equips a clinician with the background essential for clinical work. However, there remains a distinct gulf between the science of neurology and its language, the medium used to interpret and communicate information about clinical features in health and disease. The purpose of this chapter is to outline some features of the practice of day-to-day neurology:

- To provide a framework for examination, clinical diagnosis and investigation;
- To mention the terminology used to capture concepts and patterns – the vocabulary of neurology; and
- To discuss some illustrative patterns essential to recognize.

Facets of the history of neurology and some subtleties of clinical practice are mentioned to provide a brief working overview.

Practical neurology is sometimes straightforward but remarkably difficult at other times. Our initial purpose as diagnosticians is to answer one question: whether or not there is a recognizable disease. In no other branch of medicine is recognition of clinical patterns more important, nor are they more reliable. Despite major advances in imaging, neurogenetics and neuropathology, clinical practice continues to follow a familiar traditional systematic approach:

- Assemble the elements of clinical observation in a structured layered fashion commencing with the simplest information, followed by physical signs and the results of appropriate investigations.
- Recognize by assessing and sifting the layers of information, the site of a lesion, its nature and/or the system affected.

Failure to follow this approach can lead to errors and especially misjudging the seriousness of a problem, either overestimating symptoms – thus leading to alarm and expense or, vice versa, missing a serious disease.

Elements of diagnosis

The components of clinical diagnosis in neurology – its essence and singularity – are the clinical history and examination and the interplay between the two. Many people find neurology hard, both because of this interplay and also because of the breadth of the subject. Few specialties deal with such a wide range of conditions.

Some neurological conditions are wholly descriptive, such as migraine or epilepsy. We rely on a narrative of the patient or an eyewitness. In other situations, neurological signs play a pivotal part, e.g. the emergence of a spastic paraparesis. A complication occurs when one pattern of symptoms or signs might be explained by pathology in different parts of the nervous system or by different mechanisms, an example being the differential diagnosis of spastic paraparesis (see below). However, despite sophistication the nervous system has a relatively limited repertoire of symptom complexes. Examples of this are:

- Four limb numbness can be similar in character whether caused by a cervical cord lesion or polyneuropathy.
- A clumsy hand can be caused by a lesion in a peripheral nerve, root, spinal cord or cerebral cortex.
- With headache, the pain of a benign headache and the pain of a serious problem may be similar.

It is the pattern of symptoms and the presence or absence of signs that enable reliable diagnosis.

Diagnosis is a two stage process:

1. Do the history and physical signs point to the site of the lesion or lesions?
2. Does the pattern and tempo of symptoms point to a recognizable disease?

History

The narrative, from the patient, relatives or other witnesses provides primary data. This is vital information and a detailed history

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Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

of the symptoms or events at the onset of a neurological condition is often helpful as a first step towards a diagnosis. How to take the details of a present, past and family history is assumed. Three areas are mentioned where difficulties and pitfalls commonly occur.

First, vividness can only be provided by an account, taken verbatim, of events that have brought about a consultation. With the era of electronic records and abbreviation overtaking the written word, it is necessary to reaffirm the viability of simple narrative and record the story of what happened. For example, the phrase 'Fitted in bus on way to A&E – bitten tongue' is familiar medical shorthand seen in many emergency department computerized summaries. The inference is that a generalized tonic–clonic seizure has occurred. This may be the correct conclusion but to rely upon it is fraught with danger. The phrase does not indicate what the patient actually said:

> 'I was standing on the Number 73 bus near King's Cross first thing in the morning taking my mum to the hospital at University College. I felt all dizzy and sick, my eyes went all funny, then my legs went weak . . . and out I went. I came to on the floor, between the seats in a pool of blood. My mother says I fainted. But then the ambulance was called and they said I was shaking. I had bitten my lip quite badly. I was right as rain in five minutes but the lady in the ambulance said she thought I had had a fit.'

From this description of the circumstances – the brief duration of loss of consciousness and transient shaking – syncope seems likely, not the generalized tonic–clonic seizure implied by the original note. The effect of shorthand, jargon and misdiagnosis can have far-reaching consequences.

Secondly, it is important to identify the temporal pattern of symptoms, since these often provide clues to aetiology. Examples are:

- Intermittent, i.e. full recovery between symptoms. Common causes include epilepsy, migraine, transient ischaemic attacks and some rare genetic disoders such as paroxysmal dyskinesias.
- Fluctuating, chronic. MS is the typical example of a condition with this tempo.
- Progressive, chronic. Neurodegenerative and neoplastic disorders tend to follow this pattern.
- Acute or subacute progressive. These are usually infective or inflammatory disorders.
- Acute onset, single insult, with recovery. Vascular disease, i.e. stroke, is the typical example; Guillain-Barré syndrome is another.

The long time scale of some neurological conditions is important to bear in mind – for example a history of prolonged febrile convulsions in infancy may be of relevance to episodes of loss of consciousness developing in adult life.

Other aspects of the history can point to a diagnosis, such as the past medical or family history, the latter being of particular importance in many neurological conditions and frequently overlooked.

Thirdly, there is the matter of attitude, the balance between critical appraisal, sympathy and the role of the physician – and a reminder that our principal purpose is to help. Judgemental attitudes, while understandable, interfere with clinical diagnosis; they are a frequent cause of a patient or their family seeking a second opinion.

Attendance at a clinic for the first time often involves questions about very difficult emotive issues, hard to articulate. There is no such thing as a hopeless historian. The public is increasingly better and accurately informed. By contrast, the unsympathetic neurologist has been described too frequently and vividly to be discounted. Whether or not symptoms reflect a serious disease, patients do actually suffer from their complaints. That first visit frequently carries a burden – a serious diagnosis is all too often being questioned. Patients and their relatives hang hopes and fears upon single words, phrases and comments made by medical or nursing staff. Furthermore, depression, and psychiatric comorbidity are features of many neurological conditions, or effects of them. Anxiety is common in any clinical situation, serious or apparently trivial.

Nature of symptoms

Textbooks that provided the foundations of clinical practice emphasized the distinction between primary and secondary symptoms, and positive and negative phenomena. This approach needs to be understood and can be useful, although the classification is not rigid and slightly conjectural. Most anatomical brain, cord, root and nerve lesions are destructive. They cause negative symptoms of loss of function, e.g. paralysis. They may also cause positive secondary phenomena, typically features where neuronal inhibition is released, e.g. exaggerated tendon reflexes, clonus. Positive is also used to describe irritative, usually electrical phenomena such as seizures or myoclonus.

Abnormalities of function can thus be regarded in two ways:

1 Primary (direct) abnormalities, often negative: one part fails to work. Primary abnormalities can also be positive (irritative), e.g. focal seizures resulting from a cortical glioma, pain in the distribution of a trapped median nerve or hemifacial spasm.

2 Secondary (indirect) abnormalities, usually positive, often indicate over-activity resulting from release of inhibition (e.g. clonus).

Neurological examination

Preliminary assessment

Many features become apparent during conversation, during the narrative history: 'More can often be learned of a patient's disabilities by observing his ordinary actions, as dressing and undressing, walking when apparently unobserved . . . than by specific tests' was written by Gordon Holmes in 1946. We rely heavily on this apparently casual approach on a daily basis. It is the way we form an impression when meeting a new person, our own friends and colleagues, either socially or professionally. There is much to be learnt from perfecting this method of data gathering before more formal examination – provided one is not judgemental. We all use such skills but can usually refine them. The following can be readily appreciated during the history prior to more formal examination on a couch:

- Greeting, manner, orientation, attention, mental state, mood, personal hygiene;
- Cognitive conversational clues – e.g. the mildly cognitively impaired patient turning towards a relative to answer a simple question;
- Speech, language and facial appearance;
- Gait and stance;
- Clumsiness, weakness of one side;
- Involuntary movements;
- Patterns of sensory symptoms;
- Evident risk factors, lifestyle, tobacco, alcohol, drug abuse;
- Obsessions, religion, illness beliefs, fears;
- Full details of episodes of disturbed consciousness, headaches, transient events;
- Degree of disability, aids – both in the home and outside, state benefits;
- Aspects of daily living, travel, driving, employment, dangerous sports;
- Evident endocrine or general medical clues;
- Relations with and attitudes to hospitals, practice staff and other specialists;
- Expectations and ideas about treatment.

Brief neurological examination

It is assumed that the reader can carry out a general examination and understands the rudiments of neurology. Detailed neurological examination for every case is simply impracticable in busy clinical life. In many settings we must learn to rely on a brief, robust, safe and practical examination tailored to the individual, and be guided by the history. The man who fainted on the bus does not need two-point discrimination to be assessed. A tendency to dwell on excessive detail of examination seemed to beleaguer generations of neurologists. Table 3.1 illustrates a brief neurological examination, completed easily within 5 minutes and readily adaptable to circumstance.

Detailed neurological examination

More detailed examination is sometimes necessary; the finer details of a full examination are valuable when complex cases are investigated. A scheme developed at the National Hospital is widely used and adapted into Table 3.3. Quite simply, this helps to avoid forgetting important data and records information for future readers. The order of examination presented here is the way in which most neurologists work and it is thus helpful to follow it.

Cognition and mental state

Much will have taken place during the clinical history. A record of a Mini Mental State Examination is a useful way to record the situation in appropriate cases. Many versions are in use (Table 3.2).

Table 3.1 Typical brief five part neurological examination.

1 Look generally at the patient	**4 Lower limbs**
General demeanour	Tone
Speech, language, cognition	Power (hip flexion, ankle dorsiflexion)
Gait, heel–toe, possibly Romberg's test	Coordination
Arm swinging	Reflexes
	Plantar responses
2 Head	**5 Sensation**
Fundi	Simply ask (in most cases): is it normal?
Acuity (if appropriate)	
Pupils	
Eye movements	
Facial movements	
Tongue	
3 Upper limbs	
Posture of outstretched arms	
Wasting, fasciculation	
Tone, power	
Coordination	
Reflexes	

Such an assessment combined with an appropriate general examination including blood pressure is highly unlikely to miss serious disease.

Table 3.2 Mini Mental State Examination.

Orientation	
Year, season, date, day, month?	(5 points)
Country, city, area, house number, street?	(5 points)
Registration	
Name three objects: 1 second to say each	
Ask the patient to repeat them	(3 points)
Repeat until the patient has learnt all three, count trials and record	
Attention and calculation	
Serial 7s: 1 point for each correct. Stop after five answers	(5 points)
Alternatively, spell 'world' backwards	
Recall	
Ask for names of the three objects repeated above	(3 points)
Language	
Name a pencil and a watch	(2 points)
Repeat the words: 'no ifs ands or buts'	(1 point)
Follow a three-stage command	(3 points)
Read and obey the following: 'Close your eyes'	(1 point)
Write a sentence	(1 point)
Copy a design	(1 point)
Total score	**(out of 30)**

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Table 3.3 Detailed neurological examination.

Historical details

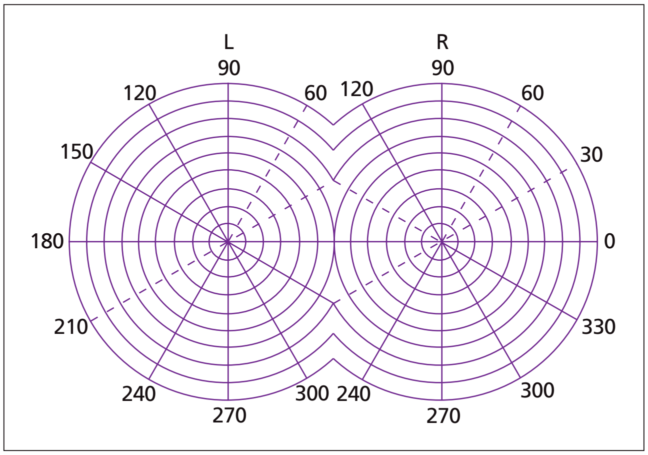
Main complaints
History of present illness
Past illnesses
Review of previous opinions, practice notes, etc.
Family history, with details of size of family
Social, personal, alcohol, drugs, tobacco, etc.
Travel, occupation, etc.
Review of systems:
- cardiovascular
- respiratory
- gastro-intestinal
- genito-urinary
- endocrine
- psychiatric history
- allergies – drug and other

Examination

Physical appearance, initial appraisal
Mental state and cognition, mini mental state examination
Speech, language functions, evidence of higher function problems
Skull and spine
Gait, stance, balance
Hand preference – writing, etc.

Cranial nerves

I. Olfaction
II. Visual acuity
Visual fields – describe/chart
Describe/chart



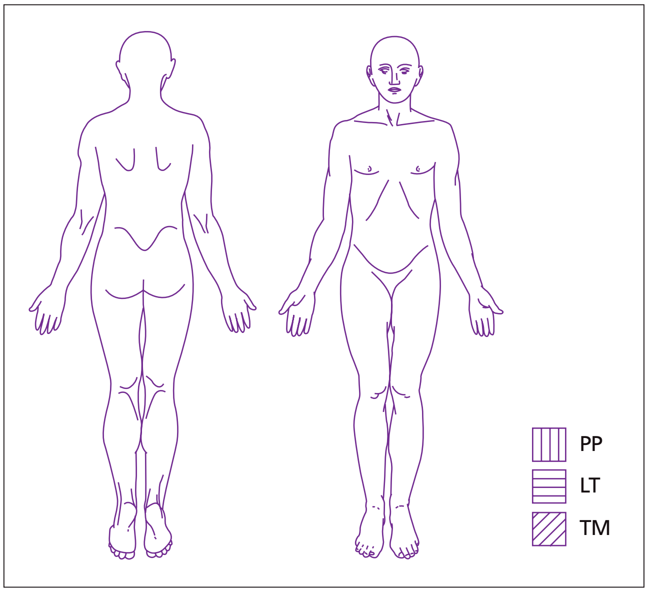
Fundus
Pupil (mm, shape, reactions)
III, IV, VI. Range of ocular movements, nystagmus
Inspection of each eye, proptosis, cornea, primary position of gaze
V. Facial sensation, corneal reflexes, jaw movement (masseter, temporalis), jaw jerk
VII. Facial symmetry, weakness, abnormal movement, taste
VIII. Hearing, Rinne, Weber, vertigo, nystgamus
IX, X. Swallowing, phonation, gag reflex, pharyngeal sensation
XI. Sternomastoids, trapezii
XII. Tongue appearance, speed, central protrusion, fibrillation

Motor system

Abnormal movements – describe
Posture of upper limbs – describe
Tone
Power
MRC Scale 1/5 and/or describe wasting, fasciculation, muscle consistency
Assess limbs, neck, diaphragm, abdomen
Coordination (finger–nose testing, alternating movements, foot tapping, etc.)
Reflexes:
- jaw jerk
- biceps jerks
- supinator jerks
- triceps jerks
- finger jerks
- abdominals (upper and lower)
- knee jerks
- ankle jerks
- plantar responses
- other reflexes (state)

Sensation

Assess: 1. Posterior columns: vibration (128 Hz, VS), joint position (JPS), light touch (LT), 2-point.
2. Spinothalamic: pain (PP), hot/cold (TM),
Chart findings: PP, TM, LT, etc.



General physical examination

Cardiovascular, BP, respiratory, abdomen, endocrine, skin, nodes, joints

Summary of findings

Formulation

Provisional diagnosis

More detailed screening tests are readily available. The Queen Square Cognitive Screening Tests are used widely; there are many others. These assess:

- Orientation and alertness;
- Language;
- Literacy;
- Praxis;
- Memory; and
- Right hemisphere function.

These screening tests provide an accurate assessment in a clinic or at the bedside and can be confirmed and explored by further detailed clinical psychometry (see below and Chapter 7).

Episodes of disturbed consciousness are discussed in Chapter 6, and coma, stupor and similar states in Chapter 19.

Skull, scalp and spine

Skull and scalp examination is often omitted. Abnormalities of contour, abnormal circumference, old burr holes or gnarled scalp vessels without a pulse may be found. Skull bruits are best detected by the following technique:

- Ask the patient to close both eyes, gently;
- Rest the bell of an old-fashioned stethoscope over one closed lid;
- Ask the patient first to open the other eye; and then
- To stop breathing, briefly.

This manoeuvre reduces extraneous noise from lid muscles and respiration.

Examine the spine and its contour. Assess for scars, stiffness, deformity, pain, bruits and for tufts of hair, dimples, sinuses or suggestions of congenital abnormalities.

Cranial nerves

I: olfaction

Two test substances from a selection of clove oil, peppermint, mint, eucalyptus oil – or simply soap, coffee or an orange – are adequate to determine whether the patient can distinguish between (not recognize) odours. More complex olfactory test kits are becoming more widely used, e.g. in Parkinson's or Alzheimer's disease (see also Chapter 12). Ammonia is sometimes used to assess trigeminal afferent responses; such a highly irritant substance should be handled with care, or avoided.

II: vision pupils and fundi

For visual acuity measurement a well-lit 3-m handheld Snellen chart is adequate for most purposes. Correction with the patient's lenses or a pinhole (easily fashioned from paper) may be needed. A record of acuity is one hallmark of a careful out-patient letter. See also Chapter 13.

Visual field examination to finger confrontation is highly reliable for picking up hemianopic or visual attention defects. Follow this when appropriate by confrontation using a 5-mm white and 5-mm red pinhead, or other target. The visual field is not a plane: move a target along the circumference of the visual field, some 50 cm away from the eye. Commence with the target at a point lateral to, and behind the visual field – out of sight, behind the ear – and move it forward, along the circumference of an imaginary circle of some 50 cm radius, towards the midline.

Using red and white-headed pins, individual techniques of field examination vary. One suggestion is to use simple positive phrases, e.g. with a white pinhead, ask the patient to: 'Say NOW, when you see the pinhead'; with a red pinhead, ask the patient to: 'Say RED, when you see the pinhead'.

Central field defects: use an Amsler grid. Or, simply ask the patient to look at newspaper text and indicate any holes in their vision.

Colour vision is speedily assessed with Ishihara plates (still in use after nearly a century), or with detailed 100 Hue Test cards.

Pupil reactions are seen best in low levels of illumination using a bright light shone through the lens, approaching slightly from the temporal side to avoid producing convergence. Subtle abnormalities of the pupillary response to light, e.g. an early Horner's syndrome, can sometimes be picked up by darkening the room. Cross-illumination – a pen torch at right angles to the visual axis – helps light up an iris of a darker shade. Putting these two together (direct and cross-illumination), many a pupil apparently unreactive in daylight (e.g. in old age – senile miosis) can be seen to constrict, if only a little. The swinging light test, especially in dim light can identify a relative afferent defect. Other abnormalities of the pupils are discussed in Chapters 13 and 19.

Fundus examination takes experience to perfect. The crux is to develop a suitable personal technique. Suggestions are:

- Have the patient seated, gazing horizontally – not at the ceiling. Suggest they gaze at some distant object. Mention there is no problem if they blink. These manoeuvres avoid one's own clothing or hair falling into the subject's face, help fixation and discourage following the ophthalmoscope light source.
- For the left fundus, try to look through the ophthalmoscope with your own left eye and vice versa. This encourages the patient see past you and to fixate. Also, do not close your own 'unused' eye; if this is hard to achieve, cover it with a free hand. This helps the viewing eye to focus on infinity through the ophthalmoscope, and allows your face to relax.

III, IV and VI: eye movements

Recently acquired double vision is a frequent reason for urgent referral and for many doctors a distinct cause of confusion/anxiety. The latter is especially so if the 'four formal rules' for diplopia (Table 3.4) are followed rigidly for every case. An alternative, shorthand system that relies much on recognition at a glance is the reality: every experienced neurologist uses some form of this approach. Such a simple scheme diagnoses most cases quickly, i.e. most diplopia can be assessed by ascertaining whether or not the abnormality fits one of four patterns.

Table 3.4 Four rules for recognition of a weak ocular muscle.

1	The false image is usually the less distinct and more peripheral
2	Diplopia occurs in positions that depend upon contraction of a weak muscle
3	A false image is projected in the direction of action of the weak muscle
4	Image separation increases in the direction of action of the weak muscle

A tendon hammer shaft is a convenient tool for the patient to follow.

VI: abducens nerve palsy

This causes:

- The complaint of double vision with two images side by side (i.e. diplopia with horizontal separation);
- An evident convergent squint;
- Double vision that disappears on looking away from the weak lateral rectus muscle and vice versa – worse towards the weak muscle in the obviously squinting eye; and
- No abnormality in reaction to light in the pupil.

Remember that a lateral rectus palsy can be caused either by a VIth nerve lesion or by disease of the lateral rectus muscle or neuromuscular junction.

III: oculomotor nerve palsy

A complete, e.g. compressive, IIIrd nerve palsy typically causes:

- Ptosis – the lid drops, covering the eye completely;
- A pupil that is large and unreactive to direct light (the contralateral pupil constricts normally);
- An eye (on lifting the lid gently) facing down and out.

The term partial IIIrd nerve palsy usually implies sparing of the pupillary and lid parasympathetic fibres; these lie on the undersurface of the IIIrd nerve and have a separate blood supply. The pupil remains normal. Ptosis is incomplete. The eye faces down and out. A complication of diabetes is a typical cause (Chapter 25).

Internuclear ophthalmoplegia

Damage in the brainstem to the medial longitudinal fasciculus causes an internuclear ophthalmoplegia (INO):

- Disconjugate horizontal eye movements, i.e. movements not yoked together – the eyes move horizontally at different velocities. One suggestion to help observe disconjugate movement is to look at the centre of the patient's forehead – otherwise there is a tendency for the examiner to fixate on one eye and miss what is happening to movement in the other;
- Incomplete adduction of one eye – and when this is so;
- Coarse jerk nystagmus is seen on lateral gaze in the other eye, i.e. on abduction

Internuclear ophthalmoplegia is described as left-sided when there is failure of left adduction, i.e. looking to the right. There are various varieties of INO (Chapter 13).

IV: trochlear nerve palsy

A distinct rarity compared to IIIrd and VIth nerve palsies, a IVth nerve palsy causes:

- A complaint of double vision on looking down, e.g. descending stairs;
- 'Twisted' images, i.e. one at an angle to the other;
- Head tilt away from side of superior oblique muscle weakness;
- No obvious squint.

Four rules for diplopia assessment

There are numerous other varieties of weakness of the extraocular muscles and the more detailed approach becomes necessary when cases do not fit into the patterns above. The four formal rules established in the early 20th century are logical, accurate and invaluable in such complex cases (Table 3.4). Even using them, some cases of ocular muscle disease (e.g. myasthenia, ocular myopathy) can prove difficult. It is usual to track movements in the shape of an H. Lateral movements are assessed, followed by elevation and depression at about 30° of lateral gaze. A minor degree of diplopia is an almost normal finding at the extremes of gaze; blurring and 'false-framing' of objects is also easily accomplished, either in error or deliberately, by converging on an object closer than one's natural near point.

V: trigeminal nerve – sensory and motor

Most people with sensory loss in the distribution of one or more trigeminal nerve branches complain of numbness and tingling in a clearly defined anatomical zone – making the detailed assessment of pain, temperature and light touch superfluous (Figures 2.48, 3.8 and 12.1). Many people have experienced V_3 sensory loss, following lidocaine at the dentist, so there is a familiar flavour to the symptom. The main exception to this obvious, descriptive altered sensation is the imperceptible loss of corneal sensation seen with an early acoustic neuroma, or other lesion at the cerebello-pontine angle (CPA). This is initially isolated, symptomless and only found by careful technique.

Corneal reflex: technique

Approach the cornea from the lower temporal side (avoid a visual threat) with a pointed wisp of cotton wool. For ease of access, gently draw down the lower lid. Rest the wool gently upon the infero-lateral cornea, not the conjunctiva – between 6 and 9 o'clock for the right eye. Ask the patient what they feel and observe the surrounding conjunctiva for the normal reddening and tearing. Someone with an early depressed corneal reflex may say 'I can feel you touch me but it isn't painful like it was on the other side.' When the corneal reflex is depressed, conjunctival injection and tears are markedly diminished.

The fine print of corneal reflex examination is this: V_2 supplies the lower 60° corneal sector, i.e. between c. 5 and 7 o'clock; V_1 the supplies the upper 300°. This is occasionally of clinical value.

Neurologists vary in the emphasis they attach to evident blinking versus pain (a VIIth nerve blink response to corneal nociception rather than discomfort) during testing the corneal. Many find it simpler to regard practical day-to-day examination of the corneal reflex as a facet of Vth nerve sensory examination rather than a V → VII reflex; the blink response is sometimes valuable in ITU (Chapter 19).

There are several other aspects of Vth nerve examination. These relate to the distribution of the three divisions of the nerve. First, the distribution of V_1 extends to the scalp – as far as the vertex (via the supra-orbital nerve). Supra-orbital nerve lesions, often traumatic or surgical, can cause headaches. Secondly, V_3 does not supply the skin of the neck: patients with non-organic facial sensory disturbance often complain of symptoms below the distribution of V_3 (mandibular division), i.e. including skin over the neck and platysma. Thirdly, C2 supplies the posterior scalp, including the area up to the angle of the jaw. Another symptom (or sign) is common – a slight change in temperature perception between one side of the face and the other. This is rarely of significance.

Finally, central lesions (brainstem) can cause circum-oral, 'onion skin' sensory loss (Chapters 2 and 12, Figure 2.51). Any complaints of sensory disturbance around the mouth should not be dismissed.

V motor examination

Motor lesions of V are unusual, but easy to miss unless jaw deviation (to the weaker side) is assessed carefully. The easiest approach is to look at the incisor teeth. Establish the centre line of the upper and lower incisors and see if the centre line remains central or moves laterally as the jaw opens against slight resistance. At this point, some neurologists tap the jaw jerk; others tend to leave this until the cranial nerve examination has been completed.

VII: facial nerve

A complete lower motor neurone (LMN) facial palsy affects all facial muscles on one side, whereas upper motor neurone (UMN) weakness affects lower parts of the face; this spares blinking and wrinkling of the forehead. This difference between UMN and LMN lesions is explained by bilateral innervation of parts of the VIIth nuclei supplying upper facial muscles (Chapter 2). There are some subtleties of facial examination. In early UMN facial weakness, all that may be evident is a hint of slowing or delay of a blink, spontaneous grin or grimace. There may be dissociation of voluntary and involuntary movement: formal 'show your teeth' examination can remain normal, but a spontaneous smile slow on one side.

For LMN lesions, divide up the face and suggest definite actions:

- *Frontalis:* 'Look upwards' usually produces furrowing the brow – the response required. A 'wrinkle your forehead' suggestion produces a variable grimace;
- *Orbicularis oculi:* try: 'Screw up your eyes tightly';
- *Alae nasae:* 'Wrinkle your nose';
- *Orbicularis oris:* 'Now try to whistle gently';
- *Risorius* (and others): 'And now please show me your teeth';
- *Platysma:* men who use a razor find this muscle easy to demonstrate – they tension the skin of the neck. With women, eversion of the lower lip is said to be one way to demonstrate platysma; another is a suggestion to: 'stick out your chin and grunt' – either seems inappropriate. Attempting to copy the examiner usually solves the problem.

Involuntary movement of the face, e.g. myokymia (see below and Chapter 12), fasciculation and minor degrees of hemifacial spasm can be hard to see. Illuminate the face well, and look closely.

Finally, as a practical point, the gradual emergence of patchy facial weakness is distinctly unusual in Bell's palsy – the most common cause of acute LMN weakness. If the facial weakness is minor or develops gradually over weeks, suspect some other, possibly sinister cause. In Bell's (Chapter 12) weakness is usually at its worst within 12 hours; there is frequently pain around the mastoid, hyperacusis and loss of taste.

VIII: auditory nerve

Testing is often unnecessary when there is no problem with hearing. If there is a degree of hearing loss, record the distance at which a whisper (or speech) is heard. The Rinne test is excellent for conductive deafness but of less value for the sensorineural deafness of particular interest to a neurologist.

Here is a simple pragmatic approach to the assessment of hearing:

- Record the distance a whisper is heard from the ear;
- Occlude gently both external auditory meati with the tips of each index finger. Rustle with each middle finger the skin/hair over the mastoid. This provides a rough-and-ready measure of bone conduction. If there is an evident difference between each ear, perceptive (sensorineural) loss is usually present. It is remarkable how accurate this is.

Rinne and Weber tests are discussed in Chapter 14. In practice, any suspicion of a CPA lesion will be followed up by detailed MR imaging and specialized audiometry.

VIII: vestibular nerve

Dizziness, vertigo and nystagmus are dealt with in more detail in Chapter 14. The basic balance tests are observation of gait and station, and Romberg and Unterberger tests (R+U). Opinions vary about the value of these latter two, named tests. One view is that they are obsolete, pointing out that injuries occur if the tests are carried out carelessly. The Romberg test (Dr Moritz Heinrich Romberg, 1795–1873) was originally of value in the diagnosis of tabes dorsalis. In this variety of neurosyphilis, joint position sense became so severely impaired that the patient would lurch wildly on closing the eyes. The Unterberger test ('Stand to attention with arms extended forwards, march on the spot and close the eyes') is a non-specific test developed in 1938 of either vestibular or cerebellar problems – the patient turning towards the side of the lesion. One, perhaps cynical, view of these tests is to record theatrical responses in those with no organic disease – but in these cases particular care must be taken to avoid injury. Most find R+U tests of some value – Romberg's is useful for detection of subtle proprioceptive losses.

Nystagmus and vestibular testing are considered in more detail in Chapter 14. A common error is to over-diagnose as pathological a few beats of nystagmus at the extremes of lateral gaze – this is normal. Nystagmus must usually be sustained, and well within binocular gaze, to be pathological.

IX and X: glossopharyngeal and vagus nerves

Take these nerves together. Observe the uvula and fauces on saying 'Aaah'. Look for pooling of saliva and residual food remnants. Most neurologists no longer use the gag reflex alone as a measure of safety for swallowing. Many patients with an intact but hyperactive gag continue to swallow, but do so in a disorganized way and may aspirate; others with a depressed gag are shown on videofluoroscopy to swallow safely without aspirating. If there is a question of bulbar weakness or difficulty swallowing:

- Listen to the voice – this sounds 'wet' in the early stages of bulbar muscle weakness (Chapter 12);
- Ask the patient to cough;
- Look for deviation of the palate/uvula (away from the side of the lesion);
- Watch the patient begin to drink a glass of water, if this seems safe and look for spluttering, choking and pooling after a mouthful.

An isolated IXth nerve palsy – a rarity and hard to identify – causes impaired sensation on one side of the pharynx. Tickling the area with a cotton wool bud in the normal person causes discomfort and elicits gagging, via the vagus. In many patients, there is little need to test the gag reflex.

XI: accessory nerve

The most common cause of an isolated spinal accessory nerve lesion is a surgical complication of biopsy of a node in the posterior triangle of the neck. The nerve is superficial here and easily damaged en route to trapezius. Weak shoulder shrugging is seen. Weeks or months later, pain around the shoulder and upper scapula frequently develops – typically an intense intractable neuralgia. While examining trapezii and sternomastoids, look for winging of the scapula and at the neck muscles (Chapter 12).

XII: hypoglossal nerve

Tongue wasting and deviation to the weak side when protruded is the well-known sign of a unilateral XIIth nerve lesion. It is also useful to look at tongue movement generally. The speed and amplitude of tongue movement are diminished in bilateral pyramidal lesions and often early in Parkinson's disease. Tongue fibrillation, seen in motor neurone disease, should be diagnosed only when the tongue rests within the mouth. A few twitches of tongue muscles occur in normal people when the tongue is protruded.

Gait and disorders of movement

The pattern of walking and any major abnormal movements should have been noted in the initial appraisal. It is useful to reflect on that first impression and to carry out more a detailed analysis, either here or at another point in examination.

Record whether gait is:

- Normal and symmetrical without limp, or abnormal, perhaps in some ill-defined way;
- Spastic – narrow-based, stiff, toe-scuffing;
- Hemiparetic;
- Extrapyramidal – shuffling, festinant (hurrying), with poor arm swinging, or simply very slow;
- Apraxic – e.g. with gait ignition failure, or with walking difficulty but with preserved ability to move the legs rapidly whilst on a bed, or seated – normal bicycling movements;
- Ataxic – broad-based, unsteady;
- High stepping, foot drop, myopathic, antalgic, neuropathic; or
- Unusual in any other way, e.g. affected by disorders of movement, such as dystonia, chorea or myoclonus – or apparently theatrical and non-organic.

It is feasible to categorize most gait problems by observation, e.g. spasticity, chorea, festination, dystonia; but the real issue here is to avoid missing something subtle yet really quite evident. For example, fidgetiness of early chorea can easily pass unnoticed unless considered. Early dystonia is easy to miss. Many gait disorders labelled initially as non-organic or even deliberate turn out to be due to an organic movement disorder. A brief video – with permission – can be helpful.

Motor system

Limb function and motor abnormality is a pivotal part of neurological examination. This is an area where eponyms became attached to hard physical signs – Babinski being the lasting example.

Posture of outstretched upper limbs

The posture of the outstretched upper limbs is one useful way to begin. The manoeuvre establishes physical rapport with the subject and if you are an examination candidate demonstrates an understanding of neurology. The test provides a wealth of information.

Ask the patient to extend the bare arms symmetrically, palms uppermost, and then close the eyes. Upper limb wasting and abnormal movements become evident. Drift with pronation and descent towards the midline is a cardinal early sign of a pyramidal lesion – as valuable diagnostically as an extensor plantar. Postural tremor may appear. Rest tremor can vanish. Chorea, pseudochorea (seen in denervation and parietal lesions) and asterixis in hepatic disease may become apparent.

Gentle downward pressure is then applied at the wrists, and released. Rebound on one side suggests a cerebellar lesion.

Fatiguability of myasthenia appears as inability despite effort to maintain the arm outstretched horizontally (the basis for the arm outstretched duration test in myasthenia).

Non-organic weakness is often accompanied by aimless waving around.

Finally, the hands and nails can be examined.

Tone

The difference in character between pyramidal increase in tone (spasticity) and the rigidity of extrapyramidal disease requires two distinct examination techniques.

In Parkinson's disease the extrapyramidal lead pipe rigidity is detectable throughout the range of movement of a joint. Begin with the wrist, and take the hand through passive, slow, deliberate extension, flexion and rotation movements, so that the wrist joint is moved throughout its range. This elicits early signs of stiffness in forearm muscles and 'cogwheeling'.

By contrast, in limb spasticity, the early pronator catch or the beats of emerging ankle clonus will become apparent, but only if sought by brisk passive movements – supinating the forearm or dorsiflexing the ankle. Slow passive movements will miss these early pyramidal signs. Spasticity increases in line with the rate of passive movement. A catch of increased tone becomes apparent before demonstrable sustained clonus can be diagnosed, i.e. when there are four or more beats of clonus at the ankle.

Power

Various scales have been devised to record weakness, including suggestions for a 10-point system; the six-point, MRC 0–5 Scale is usually used (Table 3.5). This has two substantial limitations: the inability to record numerically a slight loss of power, and its dependence on effort/cooperation. A brief description, e.g. 'I could just overcome hip flexion' deals most effectively with a slight degree of weakness. 'Give-way' weakness implies poor effort. Testing skilled hand (and foot) movement is also important: ask the patient to play an imaginary piano and/or touch sequentially with the tip of the thumb the fingertips of the fifth, fourth ring and index fingers, back and forth. This is a useful test of pyramidal function.

Table 3.5 Six (Medical Research Council) grades of muscle weakness.

5	Normal power
4	Active movement against gravity and resistance
3	Active movement against gravity
2	Active movement with gravity eliminated
1	Flicker of contraction
0	No visible muscle contraction

Note: these UK Medical Research Council grades [0/5 to 5/5] were designed to record change in power during poliomyelitis. Although most applicable to LMN weakness they remain widely used.

Fatiguability should be assessed by repeating a movement if the story suggests this might be present. The slow relaxation of myotonia should also become apparent – provided one remembers to consider it.

Focal or general muscle wasting, fasciculation and muscle consistency should be assessed.

Coordination – cerebellar signs

Signs of early cerebellar disease (Chapter 16) may be suspected during initial assessment, e.g. recognizing dysarthria or tremor, noting an ataxic gait, or rebound when examining upper limb posture. Coordination testing can commence by looking for dysmetria (past pointing) and action tremor.

When testing for dysmetria, the patient is asked to place their forefinger on the point of a tendon hammer shaft, held at the limit of their reach, and then to touch the tip of their nose. For the next cycle, move the tendon hammer slightly to a different position. The finger–nose test is a not a measure of speed, although one frequently hears the suggestion: 'Do this as fast as you can.' Carrying out the test rapidly tends to miss early cerebellar signs.

Follow with a sequence of other cerebellar tests. Individual neurologists develop their own favourites. In early disease, one test will frequently be more abnormal than others – not itself a sign of localizing value, but an indication that a single cerebellar test is insufficient. For example:

- Circular polishing of the dorsum of the opposite hand with a single finger;
- Alternating forearm pronation and supination. Show the patient this test: with forearm vertical, make a rotational back-and-forth movement. Next, repeat the test with the forearm horizontal and palm uppermost. Again, show the patient how pronation–supination is combined with tapping the fingertips of one hand, back and front on the dorsum of the opposite hand.

The clumsy term dysdiadochokinesia is used to describe abnormality in this test, distinguishing it from dysmetria. More practical tests, such as screwing in a light bulb, are also sometimes helpful.

In the lower limb heel–shin test, ask the patient to:

- Raise one leg, touch the opposite ankle with the heel; and then
- Repeat this circular sequence of movement, i.e. raising the leg again. Simply gliding one heel up and down the opposite shin will miss early ataxia.

Foot tapping (against the palm of the examiner) is another useful test that brings out disordered lower limb coordination. In cerebellar disease, eliciting knee jerks with a pendular pattern, i.e. slow and swinging when the legs are dangled vertically over the couch, or finding the absent knee jerks sometimes seen in ataxic conditions, are rarely of much diagnostic value.

Cerebellar dysarthria is usually evident without resorting to asking the patient to pronounce 'West Register Street' (in Edinburgh) or 'baby hippopotamus' – but these phrases remain deeply etched into teaching.

Table 3.6 Interpretation of tendon reflexes.

Symbol	Description	Inference/notes
0	Absent with reinforcement	Almost always pathological
+/–	Present with reinforcement	Sometimes normal, but may be pathological
+	Present	Normal
++	Brisk	Normal
+++	Very brisk	Pathological if tone is increased; may be a normal finding
CL	Clonus	>3 beats of ankle clonus = pathological; 2 beats allowed

Do not miss the slow relaxing reflexes of hypothyroidism.

The nystagmus of cerebellar disease rarely occurs without other cerebellar features. Finally, remember that midline cerebellar disease (vermis lesions) can cause gait and trunk ataxia without cerebellar signs in the limbs.

Tendon reflexes

Strictly, these are the deep tendon reflexes (DTRs of US texts). The full-size tendon hammer (approximately 33 cm [13 in] shaft) is the preferred tool; miniature versions are discouraged. A soft rubber O-ring on the hammer is preferable to hard one. Make sure the patient is relaxed – with the head and thorax resting comfortably on the couch. The 0 to +++ and CL nomenclature is shown in Table 3.6. Minor degrees of reflex asymmetry are common in normal people, as are relatively reduced knee jerks compared with ankle jerks, and sometimes vice versa. Table 3.7 indicates spinal levels of the tendon reflexes.

Reinforcement, the method of attempting to elicit tendon reflexes that are at first sight absent, is achieved by several actions. One is to ask the patient to clench their teeth and then relax; another is to clench the hands. The original Jendrassik manoeuvre is to hook the fingers each hand together and pull firmly (Dr Ernö Jendrassik, 1858–1921, Budapest). Areflexia without other physical signs is not in itself an absolute abnormality, but is usually pathological.

Extensor plantar (Babinski) and Hoffmann reflexes

Dr Joseph Babinski (neurologist, Paris, 1857–1932) wrote the 26-line description entitled the 'phénomène des orteils' (toe phenomenon) in 1896. This, the extensor plantar response, is an indication of an UMN lesion of the brain or spinal cord. Babinski is said to have used a bodkin, a sharp instrument, originally an arrowhead, but an orange-stick is now the usual instrument. The crux of the matter is that if a reproducible upgoing toe can be produced by any reasonable stroking action on the sole, then this is abnormal. There are over a dozen additional ways to elicit a similar phenomenon, many eponymous, such as Chaddock, Gordon, Oppenheim and Gonda signs; none rivals the original Babinski.

Extensor plantars are exceptional in the normal adult, but are occasionally found. Dr Johann Hoffmann (neurologist, Heidelberg, 1857–1919) described finger reflex hyper-reflexia on flicking the thumb or forefinger. This is little used by most neurologists today; in practice, other UMN signs are usually evident.

Table 3.7 Spinal levels of tendon reflexes.

Spinal level	Reflex
C5–6	Supinator
C5–6	Biceps
C7	Triceps
C8	Finger jerks
L(3)–4	Knee
S1	Ankle

Superficial abdominal reflexes

Superficial abdominal reflexes are elicited by gentle stroking with an orange-stick. This evokes a subcutaneous twitch in each upper and lower abdominal quadrant in the normal subject. There is no need for the stimulus to be sharp or noxious. The superficial abdominal reflexes are lost with pyramidal lesions. They are sometimes hard to elicit, or may be absent in the obese, or following abdominal surgical or other scars. The level of absence of lower abdominal reflexes can help confirm a thoracic level in cases of cord compression (the umbilicus is at T10).

Respiration, the diaphragm and abdominal muscles

Respiration and the diaphragm can be assessed at the bedside, by observing inspiration and expiration, and the abdominal muscles. Selective weakness of the diaphragm causes paradoxical upward movement of the umbilicus; this is well seen with the patient supine during sniffing. If there is any question of respiratory failure, a prompt assessment of respiration is essential, e.g. measurement and monitoring of vital capacity, blood gases and chest X-ray.

Lower and upper motor neurone lesions

The features differentiating LMN and UMN lesions are outlined in Table 3.8. In UMN (pyramidal) lesions, the pattern of weakness is sometimes of value diagnostically. In the lower limbs, there

Table 3.8 Lower and upper motor neurone lesions.

Feature	Lower motor neurone	Upper motor neurone
Focal muscle wasting	Visible	Absent
Fasciculation	Visible	Absent
Fibrillation potentials	Recordable on EMG	Absent
Tone	Flaccid/normal	Increased/spastic type
Weakness pattern	Segmental, nerve or distal	Pyramidal + dexterity ↓
Specific tendon reflexes	Depressed/usually absent	Exaggerated
Clonus	Absent	Present
Superficial abdominal reflexes	Present	Absent
Plantar response	Flexor (normal)	Extensor

is disproportionate weakness of hip flexors, knee flexors and ankle dorsiflexors compared with their antagonist muscles, while in the upper limbs, all extensors and finger abduction are weaker than flexors and finger abduction. This is usually accompanied by reflex changes. In early UMN lesions, not all the features of Table 3.8 need be present. In a very early lesion, loss of finely skilled finger and toe movements, or simply drift of an outstretched arm can be the only sign of abnormality.

Sensory system

Sensory abnormalities are rarely found when the patient is articulate and there are no sensory complaints or other signs. Try to focus examination anatomically.

Assess first the posterior columns – vibration and joint position sense (VS and JPS). Then move to the spinothalamic tracts. This is an anatomical approximation, but it is useful.

- Test VS at the ankles using a 128 Hz tuning fork. Familiarize the patient with the test by placing the heel of the vibrating fork on the sternum.
- Test toe and then finger JPS – holding the sides of the digit, and taking it through the smallest movements.
- Quantification of JPS is achieved by recording responses at the toes, ankles and knees – and similarly in the upper limbs. VS can also be quantified similarly, to include recording its absence at the xiphisternum or even at the clavicles.
- Examine spinothalamic sensation first with cold metal and/or a disposable sharp object – not a needle or pin.
- Test light touch with a finger tip or cotton wool. Avoid stroking or tickling; these are related to spinothalamic modalities. Detailed touch tests with fine hairs of various calibres are obsolete.
- Chart areas of sensory loss or altered sensation. In loss of sensation move from the anaesthetic area to the area of normal sensation. In hypersentivity states move from normal skin towards hypersensitive skin.
- Two-point discrimination (0.5 cm on finger tips, 2 cm on feet) is useful for completeness if circumstances warrant it. A paperclip can be easily bent into a makeshift two-point tool if traditional discriminator forceps are not available.

Two areas of sensory examination require particular attention to detail:

1 Determination of a thoracic sensory level in a possible spinal cord lesion; and

2 Charting of areas of possible dissociated sensory loss in a suspected central cord lesion such as syringomyelia.

In an early compressive cord lesion, a distal sensory disturbance may not be a significant complaint. For example, if signs of a mild spastic paraparesis are found during motor and reflex testing, check sensation on the thorax and abdomen with care. Move up from the lower limbs, first to the lower abdomen using a cold tuning fork blade and ask if sensation changes. In the normal person (test it on yourself), sensory perception changes slightly at the groin, lower costal margin and again around the clavicle. Changes at other levels, with altered diminished sensation distally, may well be pathological. The level of a cord lesion can be determined in this way. Be aware that on the thorax, a sensory level on the back is typically slightly higher than on the front.

In syringomyelia, sensory loss may also be unrecognized by the patient. Painless burns or painless minor injuries should be noted. The areas of dissociated spinothalamic loss on the trunk and upper limbs can be bizarre, conforming to no obvious pattern, because the syrinx involves the crossing spinothalamic fibres in the central grey matter of the cord. Look also for loss of sensation to a sharp object on the posterior scalp (C2).

Generally, when complex sensory loss is questioned, it is a good plan to note the initial findings and return to the patient and re-examine after an interval specifically for sensory signs.

Formulation and diagnosis

Drawing together historical data and physical signs is an essential part of assessment but frequently skimped. To conclude that a fall with loss of consciousness and residual weakness is 'collapse ?cause' or 'probably a fit', an evident hemiparesis is 'a CVA' or a complex headache history 'migraine' (common comments in A&E notes) are not formulations any medically qualified person should reach. A structured approach is essential, teasing out features from the history and building in signs found on examination in an attempt to reach either a diagnosis or at least a direction for investigations. Such attention to detail can be hard in an emergency setting, but it is in acute neurology that many mistakes tend to occur. For example, cases of sudden headache are discounted as benign when the reality is a subarachnoid haemorrhage. This is not uncommon; a careful history and thoughtful appraisal can usually produce the correct answer, and usually safe management. Another common error is the distinction between a seizure and syncope; mistakes follow easily if one fails to adopt a simple, structured approach.

As a generalization, the history often points towards a pathological process, while examination either simply confirms one's suspicions or suggests a more precise anatomical localization of that process.

Difficulties with the history and examination

It can be hard to sort out the secure details within the history, and hard physical signs and to distinguish these from less diagnostic but entirely real symptoms that have no serious underlying pathology. It is also sometimes taxing to formulate a diagnosis. However, it is necessary to try. Incomplete and sketchy formulation and omission of simple clinical information are the failings that occur most frequently. Lack of medical knowledge is seldom a problem.

To counter this, it is suggested that definite historical details and physical signs (e.g. a tonic–clonic seizure, sustained ankle clonus + extensor plantars) are separated from the less clear (vague weakness, dizziness without vertigo) and that localization and diagnosis are based on what is reasonably certain. Also, be prepared to recognize, accept and record uncertainty – it may not be clear whether the blackout was a fit or faint. It is obvious that this is advice easier to write than to practice.

Diagnostic tests in clinical neurology

In clinical neurology, as in many braches of medicine, the substantial majority of laboratory and other tests do not alter the course of a disease. However, we are surrounded by a world of technology, by tests that have illustrated features of conditions that were once unknown, by defensive practice and the need to provide reassurance that all has been done to eliminate conditions of a sinister nature. Over-investigation and screening tests have become common. It is essential to be aware of the cost–benefits of investigations and to attempt to target studies for some real purpose. The principal investigations of neurology are outlined here.

Imaging

There has been a revolution in clinical imaging. It is a salutary to recall that the first patient imaged by computerized tomography (CT) was in 1971 in London and for those in clinical practice before the 1980s, CT scanning was a novel test, sparsely available. At that time, carotid and vertebral angiography, air encephalography and myodil myelography were the standard investigations, and those only within specialist units. The human brain was first imaged by magnetic resonance (MR) in Nottingham, UK in 1978, while today, MRI is widely available; functional MRI (fMRI) is beginning to be used in clinical practice. The basic principles of modern imaging techniques, their roles and limitations are mentioned here.

Computerized tomography

A collimated X-ray beam moves synchronously across a brain slice 2–13 mm thick. Transmitted X-irradiation from one pixel, an element <1 mm^2, is computer processed and a number (Hounsfield number) assigned to its density (air = −1000 units; water = 0; bone = +1000 units). Differences in attenuation (density) between air, bone, brain and CSF enable recognition of normal and abnormal tissue – infarcted brain, tumour, extravasated blood, oedema and abnormal bone. Enhancement with IV contrast media delineates areas of increased brain blood supply. Detailed cuts through bone outline fractures and lesions within the skull and spine.

CT scanning well demonstrates:

- Most cerebral tumours;
- Most intracerebral haemorrhage and infarction;
- Subdural and extradural haematoma;
- Free blood in the subarachnoid space;
- Lateral shift of midline structures and displacement/enlargement of the ventricular system;
- Cerebral atrophy;
- Intracranial calcification;
- Skull and scalp lesions; and
- Spine and spinal cord (and CT myelography)

CT remains a sensitive imaging test for subarachnoid haemorrhage and for skull lesions.

Limitations of CT

- Lesions under 1 cm diameter may be missed.
- Lesions with attenuation similar to that of brain are poorly imaged (e.g. MS plaques, isodense subdural haematoma).
- Grey–white matter differentiation is poor.
- Lesions with attenuation close to that of bone may be missed if near the skull.
- CT can miss lesions within the posterior fossa.
- The spinal cord is not imaged directly by CT (contrast is necessary).

Magnetic resonance imaging

MRI has rapidly become the gold standard for much clinical imaging and continues to develop. Its basis is described here.

The hydrogen nucleus is a proton whose charge creates a local electrical field. These protons become aligned by sudden strong magnetic impulses. Protons are then imaged with radiofrequency waves at right angles to their alignment. The protons resonate and spin, before reverting to their normal alignment. As this proton reversion takes place, images are made at different phases. In the scanner, tissue is subjected to a rapidly reversing magnetic field and the spin measured with each switch in field direction. Various sequences known as weightings are captured, e.g. T1, T2, T2*, STIR, FLAIR, diffusion-weighted imaging (DWI). The different sequences provide different tissue contrasts; thus imaging can be tailored to the clinical question. Gadolinium is used as an intravenous contrast medium.

MRI has advantages over CT in most areas of neurology:

- MRI distinguishes between brain white and grey matter;
- Spinal cord, nerve roots and large nerves are imaged directly;

- MRI has greater resolution than CT (around 0.5 cm – or even higher resolution, with powerful magnets);
- No radiation is involved;
- Magnetic resonance angiography (MRA) images blood vessels, aneurysms and AV malformations without contrast;
- MRI is useful in some muscle diseases, e.g. myositis, and can demonstrate wasting of skeletal muscle;
- MRI can differentiate between tissue with different contrast characteristics with more sensitivity than CT.

Tumours, infarction, haemorrhage, clot, MS plaques, posterior fossa, pituitary, foramen magnum and spinal cord are demonstrated well by MRI. Focal atrophy, for instance in hippocampal sclerosis is clearly seen.

Limitations of MRI are principally time and cost. Imaging one region takes about 20 minutes. Patients need to cooperate; claustrophobia is an issue. A general anaesthetic may be necessary. Open machines are available but produce images of lower definition than conventional magnets. Patients with cardiac pacemakers, vagal nerve stimulators or with ferro-magnetic bodies in the brain and eye cannot be imaged. Following lumbar puncture, MRI frequently shows diffuse meningeal enhancement with gadolinium for some days or weeks: this is a normal finding. Over-interpretation of changes seen with normal ageing, e.g. spinal degenerative changes, can cause difficulties.

Functional magnetic resonance imaging

Functional MRI (fMRI) depends on differential magnetic properties of oxygenated and deoxygenated blood. Active brain areas use more oxygen, thus changing the local magnetic environment. This causes change in the blood oxygen level dependent (BOLD) signal. This signal cannot be precisely calibrated, so it is usual to compare activated against control state to obtain a relative signal – or significant signal change. Other ways of using functional brain imaging responses include manipulating a behavioural variable and looking for correlated BOLD signal changes. Non-linear regional brain responses can be sought by imaging a task and control state under two or more contexts, e.g. the response to a specific memory task in the presence and absence of a memory-enhancer. Differences between between state and context are shown by a local BOLD signal change.

Clinically, fMRI is seldom requested or available for day-to-day practice, but it is used in pre-surgical mapping of language, motor and other functions to determine hemispheric dominance prior to epilepsy surgery and occasionally before brain resections for tumours. The technique has a major role in research into cognitive and degenerative disorders, into specialization within different brain areas (most notably in the visual system), into the brain networks that underlie memory, different varieties of headache and other complex phenomena. Network analyses have become highly sophisticated, allowing effects of recovery and treatment to be measured. Many new patho-physiological insights have been gained in relation to brain plasticity and recovery following stroke and traumatic injury. It is speculated that fMRI, allied to techniques such as EEG and magneto-encephalography might be used in neurodegenerative conditions, to seek out characteristic functional signatures in preclinical states.

Positron emission tomography and single proton emission computerized tomography

These functional imaging techniques track uptake and metabolism of radioisotopes. Positron emission tomography (PET) scanning is sometimes of great value in locating tumours, especially those clinically silent outside the nervous system.

Single photon emission computerized tomography (SPECT) scanning has provided some useful data in the research field and is sometimes useful in the localisation of seizures during the work-up for epilepsy surgery. SPECT has however been largely discarded as a tool in much general neurology, especially following traumatic brain injury.

SPECT scanning using ioflupane (an iodine-123 based product), also known as dopamine transporter (DaT) scanning, is becoming used to assess the integrity of the striato-nigral system. It is of some value in the diagnosis of Parkinson's disease and investigation of other extrapyramidal disorders (Chapter 5).

Isotope (99mTc-pertechnetate) imaging

This was in the past of value in the detection of vertebral and skull lesions (e.g. metastases) but is now largely superceded by MR and CT imaging.

Digital cerebral and spinal angiography

The value of and indications for these important invasive vascular techniques are discussed in Chapter 4.

Brightness-mode Doppler ultrasound

B-mode ultrasound is valuable in the detection of carotid artery stenosis and also used for imaging the orbit.

Clinical neurophysiology

Clinical neurophysiological measurement continues to play a very useful part in investigation. The tests generally available are outlined here, with notes indicating how a clinician can approach their interpretation.

Electroencephalography

Electrical potentials generated by largely synchronous activity of millions of neurones are recorded simultaneously from scalp electrodes in various complex montages usually via 16 channels. The precise sources of the rhythms first described clearly by Berger in 1929 remain somewhat elusive. The main role of EEG is in the diagnosis of epilepsy and the investigation of diffuse and focal brain diseases. EEG as a tool to localize brain pathology has largely been overtaken by imaging.

Videotelemetry, the technique that combines prolonged EEG recording for hours or days with simultaneous video recording of the patient is extremely valuable in assessment of attacks that are uncertain clinically and for the localisation of epileptic discharges during the work-up for epilepsy surgery (Chapter 6).

Specially placed EEG electrodes are also sometimes used (e.g. nasopharyngeal, sphenoidal and intracranial grid and strip electrodes and intracerebral depth electrodes) to localize a seizure focus, prior to potential surgery. EEG sleep studies and EEG monitoring in coma are discussed in Chapter 19. The principal features of the EEG are summarised here; more detailed discussion of the value of EEG in epilepsy is in Chapter 6.

Alpha, theta, delta and beta activity in normal subjects

Alpha activity seen prominently in normal subjects over the occipital lobes is an 8–14 Hz (usually 11 Hz) roughly sinusoidal waveform with amplitude some 150 µV. Typically, alpha rhythm attenuates on eye opening. Amplitude of alpha rhythm is usually slightly higher over the non-dominant hemisphere.

Theta activity of 4–7 Hz is also seen, bilaterally and usually symmetrically. In normal subjects theta activity is more prominent below the age of 30 and during drowsiness. In many brain diseases excessive theta activity appears non-specifically.

Delta activity is a slower frequency, less than 4 Hz. Delta activity lower than 1 Hz is recorded from frontal electrodes during the first non-REM sleep period. Historically, the appearance of localized delta activity when awake was of some value in the diagnosis of hemisphere tumours.

Beta activity describes a rhythm faster than 14 Hz seen normally from frontal electrode recordings. Excess beta activity is seen as an effect of drugs such as barbiturates and benzodiazepines.

EEG artefacts

Various non-pathological waveforms are usually straightforward to recognize. The most common are due to eye opening – high amplitude frontal waves caused by scalp muscle contraction and eye movement. These need to be distinguished from (for example) frontal intermittent rhythmic delta activity (FIRDA), an EEG abnormality seen in raised intracranial pressure and deep midline lesions.

Epilepsy

Spikes, or spike-and-wave abnormalities (Figure 3.1), are hallmarks of epilepsy but it should be emphasized that over 50% of patients with epilepsy have a normal routine EEG between seizures. Epileptic activity is described as generalized when it is bilateral and focal (localized) when recorded over one or more electrodes. Localized spikes point to the location of an epileptic focus, for instance to temporal lobe structures. Hyperventilation, photic stimulation and sleep may enhance EEG epileptic activity but these studies are performed less commonly now than in the past: to provoke a seizure is not without risk to the patient.

'Sharp waves' describe waveforms that are not sinusoidal and may occur in patients who have seizures but in whom epileptic spikes are not seen. An isolated sharp wave, or sparse, poorly localised sharp waves are sometimes seen in the normal population.

The value of EEG in the management of seizures, in the choice of anticonvulsant drugs and in status epilepticus is discussed in Chapters 6 and 19.

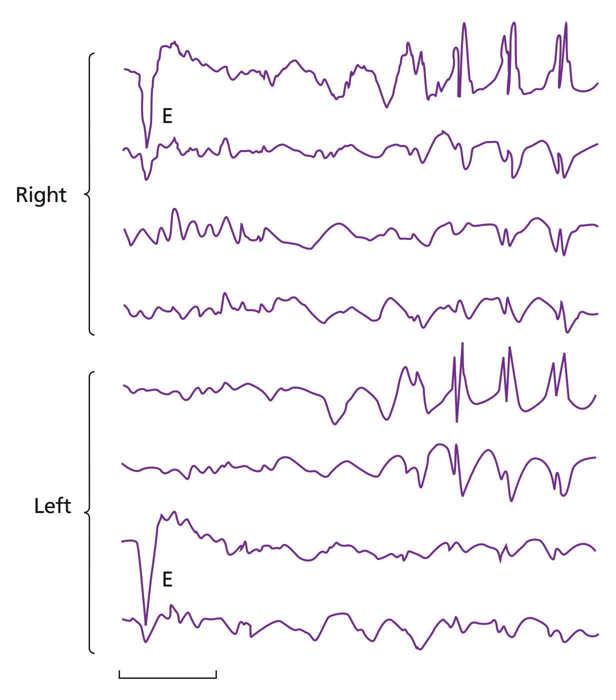


Figure 3.1 Normal electroencephalogram (EEG) activity followed by frontal spike and wave activity. E, eye movement artefact.

Diffuse and focal brain disorders

Recognizable EEG abnormalities appear in several diffuse and focal brain disorders, e.g.:

- Periodic lateralized epileptic discharges (PLEDS): seen in herpes simplex encephalitis, cerebral abscess or occasionally cerebral infarction;
- Repetitive generalized sharp waves at 0.5–1 second intervals: some prion diseases;
- High voltage stereotyped slow wave complexes, every 3–10 seconds: subacute sclerosing pan-encephalitis (SSPE);
- Triphasic slow wave complexes: seen in metabolic disorders, typically in hepatic coma.

Brainstem death

The EEG is isoelectric (flat) in brainstem death and may also be so in deep coma, e.g. with barbiturates and hypothermia. An isoelectric EEG is not necessary to confirm brain death (Chapter 19).

Clinical interpretation of EEG reports

Difficulties surround EEG reports, in part because interpretations are not standardized and in part because EEG traces can be very hard to interpret. Many clinicians will be unfamiliar with the detail of how to report an EEG and conclusions can only be drawn within a clinical context. Some useful (usually rhetorical) questions follow:

- Is there generalized epileptic activity?
- Is there localized epileptic activity?
- Is there generalized abnormal slow wave activity? If so, how specific is it?
- Is there localized slow wave activity?
- Could slow wave activity (theta, delta) reported be seen in the normal population?
- Is beta activity reported abnormal?
- Are 'sharp waves' reported truly pathological?
- In coma, is there EEG responsiveness to stimulation?
- And, finally, what can be concluded in a clinical context from this EEG report?

In an effort to mechanize EEG reporting, computerised and fractal analysis and pictorial EEG brain mapping have been employed, but none has proved generally useful in a clinical context. While EEG records are usually now paperless, written reports by the clinical neurophysiologist and technician remain the usual way in which results are presented.

Magneto-encephalography and transcranial magnetic brain stimulation

These are largely research tools used in the study of seizures and degenerative brain diseases. Transcranial magnetic brain stimulation now has a limited clinical role in central motor conduction velocity measurement. A copper coil (the magic halo) is positioned over the scalp. A current passing through the coil induces a magnetic stimulus sufficient to discharge cortical motor neurones. Muscle contraction is recorded from surface electrodes on an appropriate limb.

Clinical neurophysiological studies of nerve and muscle

Techniques of measurement and data interpretation from studies of peripheral nerves and muscle continue to advance. This is a brief overview of a complex subject. Further detail is in Chapter 9.

Electromyography

A concentric needle electrode (CNE) is inserted into voluntary muscle. The amplified recording from muscle (electromyography [EMG]) is viewed on an oscilloscope and heard through a speaker. From the CNE, three main features are seen and recorded:

1 Normal motor unit recruitment;
2 Denervation and reinnervation changes; and
3 Myopathic, myotonic, myasthenic and other changes (e.g. myokymia, cramps, hemifacial spasm, continuous motor unit activity).

Much depends upon the precise observations of the clinical neurophysiologist. Printouts of EMG traces are somewhat unhelpful compared with practical experience in an EMG laboratory, an essential element of training; with modern equipment it is usually possible to record video clips which allow review of EMG findings.

Normal motor unit recruitment

Normal muscle at rest is silent electrically although noise from motor end-plates may be heard if the CNE is placed nearby. End-plate noise is a steady 'shhhuush', not unlike 'seashell noise', and is composed of high-frequency 10–30 μV brief (<1 ms) potentials. When a single anterior horn neurone fires, all muscle fibres connected to it (i.e. the motor unit) contract. The contraction of each muscle fibre is not synchronous because of slight differences in conduction velocities down pre-terminal branch axons, giving the motor unit action potential a compound broad-based waveform lasting (depending on muscle type and age) normally up to 12 ms.

The interference pattern is the term used in EMG reports for the appearance (and sound) during muscular contraction of voluntarily activated individual motor units running together. During a gentle voluntary contraction, a single motor unit can be distinguished both audibly and on the oscilloscope. Initially, this single motor unit fires quite slowly at a rate of approximately 5 impulses/s, but at an increasing rate as voluntary contraction increases. It is then joined by a second motor unit, recognizable by its own waveform, then a third and so on. As voluntary contraction increases, more units are recruited and overlap so that individual units are no longer identifiable. This 'interference' between the units with increasing force of contraction produces the characteristic picture and sound known as a full interference pattern.

Chronic partial denervation

If one anterior horn cell (B) fails, as happens for example in motor neurone disease, adjacent anterior horn cells A and C produce sprouting axons that begin to re-innervate muscle fibres originally supplied by B. In chronic partial denervation, the EMG reflects this:

- Decreased number of motor units on voluntary contraction;
- Motor units are of larger amplitude than normal;
- The mean duration of each muscle action potential increases; new axonal sprouts conduct impulses more slowly than normal;
- Motor units may be of abnormal complexity (polyphasia); reversals of polarity are seen.

The EMG hallmarks on an oscilloscope of chronic partial denervation are thus reduced numbers of polyphasic, long duration, high voltage muscle action potentials.

Fibrillation, fasciculation, insertion activity and positive sharp waves

When a muscle is denervated, spontaneous contraction of individual fibres begins to occur, typically after some 7–14 days in limb muscles (depending on the site of lesion). These contractions produce tiny spontaneous fibrillation potentials of amplitude <10–200 μV (Figure 3.2). These have a triphasic or biphasic waveform with duration <5 ms and an initial positive (by convention displayed in the downgoing direction) deflection. In a limb, these movements of fibrillating subcutaneous fibres are invisible to the naked eye. However, in the tongue, involuntary movement of denervated fibres beneath the thin mucosa may be clearly visible (tongue fibrillation). Positive sharp waves are bi-phasic potentials with a longer duration (<10 ms) compared

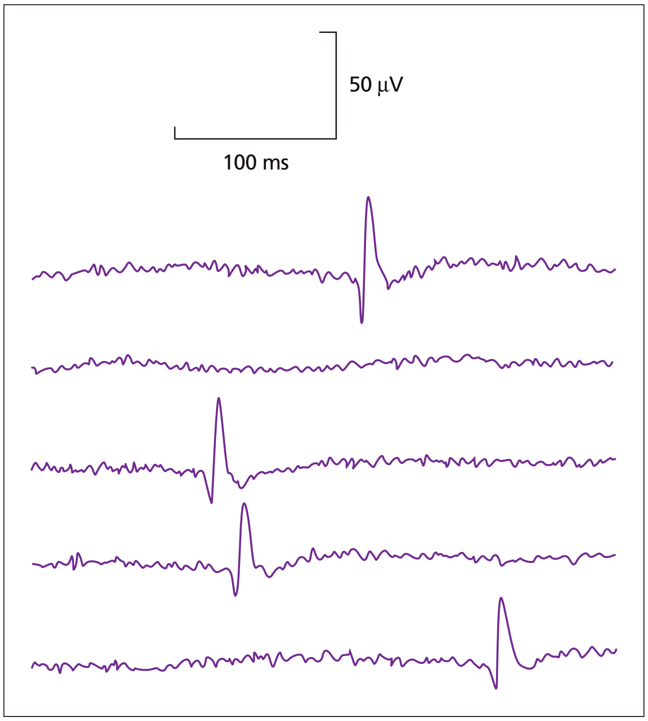


Figure 3.2 Fibrillation potentials from denervated voluntary muscle. (From Hopkins 1993, with permission.)

to fibrillations and usually with amplitudes of 10–200 μV (but occasionally, particularly when there are also chronic neurogenic changes, up to 2 mV).

Fasciculation describes the visible twitching of a muscle seen in various situations. In normal people, benign fasciculation is not uncommon in the calf muscles and may occur in other muscle groups. It is sometimes cause for concern, and particularly among those well-informed medically. In denervated muscle, fasciculation potentials having waveforms of similar dimensions to motor unit potentials are produced by spontaneous discharges of groups of muscle fibres that represent the motor unit. These cause visible persistent twitching (fasciculation), often widespread in motor neurone disease. Typically, the visible involuntary movement flits from place to place, moving on as soon as a twitch catches the examiner's eye.

Insertion activity describes the brief, <2 s volley of muscle activity provoked by the CNE impaling a muscle fibre. This volley becomes prolonged in denervated muscle, which develops exquisite sensitivity to mechanical distortion – showers of fibrillation potentials and positive sharp waves continue for several seconds after CNE insertion. Increased insertion activity describes these features of the prolonged discharges recorded from denervated muscle.

Myopathic EMG changes

Myopathic muscle has, on average, fewer than normal fibre numbers in each motor unit. As each motor unit shrinks, muscle action potentials become smaller in amplitude and of shorter duration. Surviving fibres may become sufficiently separated so that the spikes they generate do not summate to form the smooth contour of the normal motor unit. Damaged motor units are inefficient, generating less tension than their normal counterparts. Thus, for a given force, additional units must be summoned into activity. The myopathic EMG is characterized by:

- Individual units of low amplitude, of short duration and of polyphasic form;
- Rapid motor unit recruitment to a full interference pattern at lower than normal voluntary effort; and
- A recognizable crackly pattern on the loudspeaker.

Myotonic EMG changes

Myotonic muscle (e.g. dystrophia myotonica; Chapter 9) responds to mechanical or electrical stimulation with high frequency (as high as 150 Hz) action potentials lasting 2–5 seconds. The discharge frequency tends to diminish as the seconds pass producing a whine likened to a dive-bomber of propeller-driven vintage pulling out of its steep descent. A similar if softer sound can sometimes be heard through a stethoscope resting over a contracting myotonic muscle. Such dramatic EMG findings are of less critical diagnostic value than one might expect: myotonia is usually picked up clinically when power is tested. It is embarrassing for a neurologist to have myotonia recognized in the laboratory if they have missed it in the clinic – but it does happen.

Complex repetitive discharges (aka pseudomyotonic discharges) describes abnormal discharges that commence and end abruptly. These are the complex polyphasic high frequency waveforms seen in both chronic neuropathic and myopathic disorders.

Hemifacial spasm, cramps, myokymia, neuromyotonic discharges and stiff person syndrome

Hemifacial spasm (Chapter 12) is believed to be due to ephaptic transmission, i.e. transmission between adjacent facial nerve fibres. EMG shows isolated bursts of high frequency motor unit discharges of normal waveform. There is no denervation.

Muscle cramps in normal people are also seen as repetitive high frequency motor unit potential discharges typically at frequencies of 35 to 70 impulses/s. In myophosphorylase deficiency (McArdle's syndrome, Chapter 9), cramping sensations occur without these discharges.

Myokymia (Chapter 12) describes two facial phenomena:

- Quivering facial movements around the eye, common and invariably innocent, often said to be brought about by fatigue;
- Worm-like wriggling movement, persistent and usually around the chin. Such involuntary movement may be sinister and occurs in brainstem gliomas and MS.

In neurophysiological terms myokymia can be found in all muscles including facial muscles and is part of the spectrum of abnormal spontaneous activity that is generated in the motor neurone. Myokymic discharges are rhythmic grouped repetitive discharges of the same motor unit at burst frequencies of typically 5 to 60 impulses/s separated by a brief pause and repetition.

Neuromyotonic discharges are rare high frequency (>150 imp./s) discharges of a single motor unit.

In stiff person syndrome (Chapter 5), continuous normal motor unit activity or low-frequency activity is found simultaneously in opposing muscle groups, as one might expect from the clinical features. The stiffness and pattern of firing is reduced by agents acting either peripherally or centrally (curare, IV diazepam, general anaesthesia).

Peripheral nerve conduction studies

Five electrophysiological measurements are of principal value in the study of neuropathies and peripheral nerve entrapment:

1. Motor conduction velocity (MCV);
2. Sensory conduction velocity;
3. Distal motor latency (DML);
4. Sensory (nerve) action potentials (SAPs or SNAPs); and
5. Compound muscle action potentials (MAPs or CMAPs).

Accurate electrode placement and attention to detail is essential. Additional information is gained from repetitive muscle stimulation, e.g. in myasthenia. Central conduction is assessed by techniques such as somatosensory evoked potentials (SEPs) and magnetic stimulation of the motor cortex (MEPs).

Unlike EMG in which the CNE attempts to record normal or pathological physiological responses from muscle fibres, peripheral nerve conduction studies (NCS) are carried out using supramaximal percutaneous electrical stimulation. The techniques measure conduction in the fastest myelinated nerve fibres. While NCS are extremely useful, conduction measurement should be viewed as a blunt instrument compared with the finesse of EMG methodology and interpretation. Motor conduction measurement is illustrated in Figure 3.3. Tables 3.9–3.11 illustrate some typical normal values from nerves commonly tested, – such normative data are often omitted from conduction study reports, because normal values vary with age and the precise technique used.

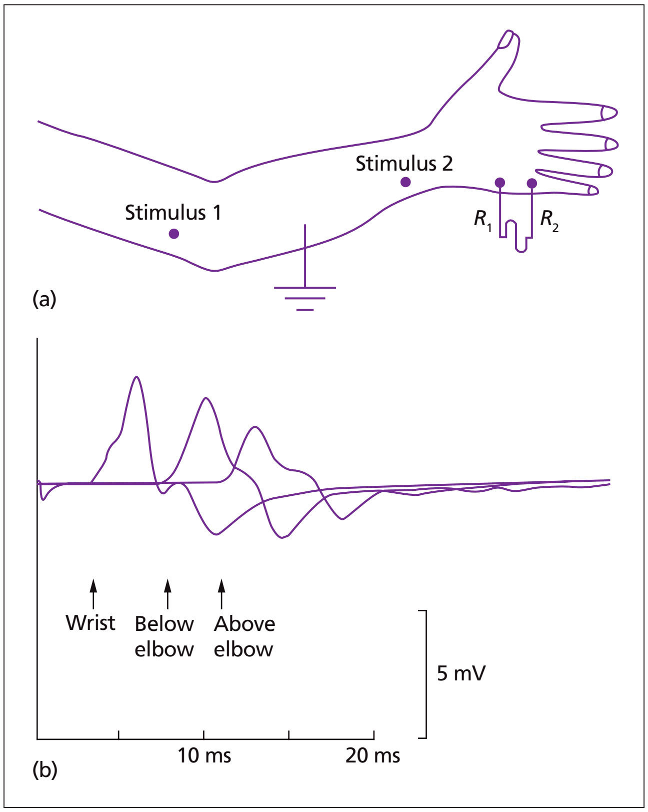


Figure 3.3 Ulnar nerve motor conduction studies: compression of nerve at the elbow. (From Hopkins 1993, with permission.)
R_1 and R_2: recording electrodes – abductor digiti minimi (ADM).
Stimulus 1 and 2: supramaximal stimuli above elbow and above wrist.
Traces: muscle action potentials MAPs from ADM from Stimulus 1, from Stimulus 2, and below elbow (stimulus not shown).
MAP amplitude from stimulation at wrist = 4.0 mV
MAP amplitude from below elbow = 3.0 mV
MAP amplitude from above elbow = 2.1 mV
MCV (calculated: distance/time) from below elbow → wrist = 52 m/s
MCV across elbow segment = 21 m/s
Conclusion: motor conduction block across elbow segment.

Polyneuropathy

In axonal neuropathies, MCV can be well preserved and there is primarily a reduction in CMAP amplitude. When the fastest conducting nerve fibres are affected there can also be a reduction in conduction velocity. SAPs are also usually lower than normal in amplitude. In demyelinating neuropathies, nerve MCV is markedly slowed, Slowing of motor nerve conduction below 38 m/s in the upper limbs and 30 m/s in the lower limbs cannot be explained by axonal dropout of fastest conducting fibres alone and is an unequivocal neurophysiological indicator for demyelination. SAPs are lost or diminished. These changes are discussed in more detail in Chapter 9.

Entrapment neuropathies

Increased distal motor latency in distal neuropathies such as in carpal tunnel syndrome, slowing of nerve conduction across the site of entrapment, such as in ulnar neuropathy at the elbow, and diminution of the relevant sensory action potential are hallmarks of nerve entrapment. Overall, MCV is preserved. Denervation changes occur in affected muscles when entrapment is severe.

F waves

These are small-amplitude muscle responses to a peripheral stimulus produced by antidromic discharges of anterior horn cells. Prolonged F wave latency or loss of F waves are seen in root lesions and in acute inflammatory polyneuropathies.

H reflexes

The H reflex (named after the neurophysiologist Paul Hoffmann, Freiburg, 1884–1962) is generated by electrical stimulation of proprioceptive afferents. Usually the tibial nerve is stimulated at

Table 3.9 Motor nerve conduction studies: normal values.

Motor nerve	Recording electrode	Amplitude (mV)*	Conduction velocity (m/s)	Distal latency (ms)*
Median	Abductor pollicis brevis	≥4.0	≥49	≤4.4
Ulnar	Abductor digiti minimi	≥6.0	≥49	≤3.3
Radial	Extensor indicis	≥2.0	≥49	≤2.9
Peroneal	Extensor digitorum brevis	≥2.0	≥41	≤6.5
Peroneal	Tibialis anterior	≥5.0	≥44	≤6.7
Tibial	Abductor hallucis brevis	≥4.0	≥41	≤5.8

* Distal latencies depend on distal distances used. Amplitudes are given as baseline to negative peak.

Table 3.10 Sensory and mixed nerve conduction studies: normal values.

Nerve	Electrodes	Amplitude (μV)	Conduction velocity (m/s)
Median*	Digit II → wrist	≥10	≥50
Ulnar*	Digit V → wrist	≥4	≥50
Radial	Snuffbox → wrist	≥15	≥50
Sural	Dorsum → ankle	≥7	≥40
Superficial peroneal	Foot → ankle	≥4	≥40
Medial plantar*	Medial foot → ankle	≥2	≥40

* orthodromic technique is traditionally used in the UK. Amplitudes for all sensory or mixed nerve studies are given as peak-to-peak values.

Table 3.11 F and H waves: normal values.

Nerve	Minimum latency (ms)
Median	F ≤ 31
Ulnar	F ≤ 32
Tibial and peroneal	F ≤ 56
Tibial	H ≤ 34

Values depend on limb length and age and there are only approximate guide for young adults of average size.

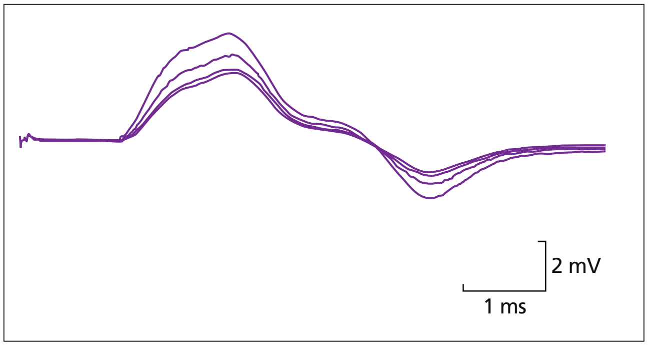


Figure 3.4 Myasthenia gravis. MAP recorded from ADM. 3 Hz stimulation at wrist. First response is 4.1 mV in amplitude. Second response is 3.2 mV. Third and fourth responses (superimposed) are 2.4 mV in amplitude. Decrement = 59% – typical of myasthenia. (From Hopkins 1993, with permission.)

the knee, and the muscle contraction of the triceps surae (gastrocnemius and soleus muscle) is recorded. This is the neurophysiological correlate of a monosynaptic stretch reflex via anterior horn cells. H reflexes are delayed when peripheral conduction is slowed, such as in polyneuropathies or in an S1 root lesion.

Neuromuscular transmission studies

Repetitive stimulation: myasthenia and myasthenic-myopathic syndromes

In myasthenia gravis a surface electrode, for example on proximal muscles such as trapezius or a facial muscle is positioned so that supra-maximal stimulation of the accessory or facial nerve, evokes the largest demonstrable response. The nerve is then stimulated repetitively at 3 Hz for several seconds. In myasthenia, if the neuromuscular junction is affected, the subsequent responses are substantially lower in amplitude than the first. This is illustrated in Figure 3.4. If repetitive nerve stimulation is not producing a decrement in a rested muscle, repetition of the investigation after an exercise for 30 or 60 seconds may do so.

In Lambert–Eaton myasthenic syndrome (LEMS), the converse is seen – facilitation (increase) of the motor response with high frequency stimulation. The amplitude of an initial response to low-frequency stimulation is lower than normal. However, repetitive stimulation at 20 or 50 10 Hz or brief voluntary contraction for 10 s produces an increment in amplitude three to four times that of the initial response. This magnitude of the response is not seen in myasthenia.

Jitter phenomenon in myasthenia gravis

In myasthenia gravis the phenomenon known as jitter can be recorded by single fibre studies. The specialized single fibre study electrode has a very small pick-up surface. Within a weakly contracting muscle, the voltage of one recorded muscle fibre potential is used to trigger the sweep. Action potentials from another fibre in the same motor unit are recorded with some delay. In normal muscle, the time difference between discharges from the two fibres remains close to constant and depending on age and muscle is often less than 50 microseconds. In myasthenia, abnormal neuromuscular transmission causes variation in depolarisation time and hence in the interdischarge interval; the second potential is seen to 'jitter' along the screen (Figure 3.5). Blocking, where one of the pair of muscle fibres intermittently fails to depolarise at all, is an expression of a more severe abnormality of neuromuscular transmission and the basis of the myasthenic decrement on repetitive stimulation, and of clinical weakness and fatiguability.

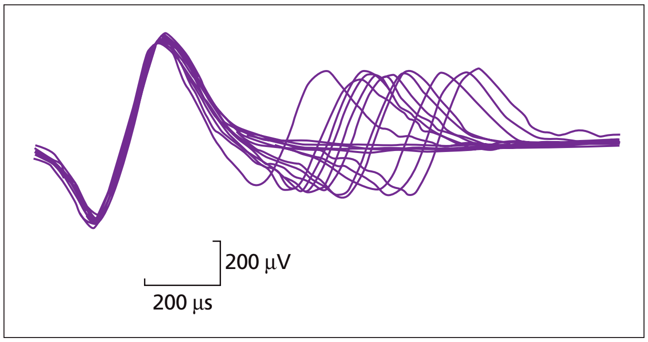


Figure 3.5 Jitter recorded in myasthenia gravis. (From Hopkins 1993, with permission.)

Cerebral-evoked potentials

Evoked potentials record the time for a visual, auditory or other sensory stimulus to reach the cortex. Visual evoked potentials measure amplitude and latency of a repetitive pattern visual stimulus to the cortex. Their value in day-to-day practice is chiefly to confirm previous retrobulbar neuritis (Chapter 10), which leaves a permanently prolonged latency despite clinical recovery. Brainstem auditory evoked potentials and somatosensory evoked responses are discussed in Chapters 10 and 14.

Specialized blood and urine tests

Much information can be gained from the routine blood tests of general medicine and these will not be dealt with here. Table 3.12 outlines some tests that may be unfamiliar to a newcomer to neurology and provides a reference base. Frequently, it is necessary to consult a clinical pathologist, microbiologist, neurogenetics laboratory or other specialist unit about specialized tests, their yield, relevance and cost (see appropriate chapters).

Cerebrospinal fluid examination

Examination of CSF – clear, colourless, almost acellular fluid around the brain, cord, nerve roots and within the cerebral ventricles – provides important collateral information about the structures that it bathes, the surrounding meninges, integrity of

Table 3.12 Some specialized tests in neurological diseases.

Clinical problem	Laboratory tests	Comments
Wilson's disease and rare cases of cord disease	Serum copper and caeruloplasmin	Extrapyramidal disorders below 40, liver disease; unexplained cord disease with normal B_{12}
Huntington's disease	CAG repeat assay	Chorea and extrapyramidal disease below 40 (see Chapter 5)
Hereditary neuropathies and ataxias	Various genetic tests, depending on features	See Chapters 9 and 16
Acquired neuropathies	Anti-ganglioside antibodies	See Chapter 9
Paraneoplastic syndromes	Anti-neuronal antibodies	See Chapters 7, 16, 20
Mitochondrial disease	Muscle biopsy, neurogenetic tests	See Chapter 9
Neurology with coeliac disease	Anti-endomysial and anti-gliadin antibodies	See Chapter 16
Leucodystrophy	Enzyme studies and genetic tests	See Chapter 18
Aminoacid metabolic disorder, e.g. homocystinaemia	Urinary and blood aminoacids	Homocystinaemia (cystathionine synthase deficiency) see Chapter 18
Adrenoleucodystrophy	Urinary very long chain fatty acids	See Chapter 18
Stiff person syndrome	Anti-GAD (glutamic acid decarboxylase) antibodies	See Chapter 5
Myasthenic syndromes	Anti-acetyl choline receptor, anti-MuSK antibodies, etc	See Chapter 9
Myopathies, dystrophies	Creatine kinase, striated muscle antibodies, genetic tests	See Chapter 9
Devic's syndrome	Aquaporin 4 antibodies	See Chapter 10
Porphyrias	Urinary porphyrins	See Chapter 18
Autoimmune limbic encephalitis	Voltage-gated potassium channel antibodies, thyroid microsomal antibodies	See Chapter 7

the blood–brain barrier and intracranial pressure. Traditionally, before the advent of non-invasive imaging, lumbar puncture (LP) and CSF examination were performed very frequently. Eponyms of that era such as the 'paretic Lange' used in the diagnosis of neurosyphilis and the 'colloidal gold reaction' are consigned to history. Today, indications for CSF examination are more specific and its role undoubted. However, the reality in observed clinical practice overall is that LP is still overused, its risks underestimated and the exceptional value of CSF examination in special circumstances neither widely understood nor are specific tests carried out with appropriate attention to detail. These notes outline the value, risks and procedure of LP and CSF examination. Cervical puncture is now so rarely performed that it will not be considered here. Ventricular CSF is sometimes examined in a neurosurgical setting, e.g. via a ventricular catheter.

Indications for LP and CSF examination

Principal indications for LP are:

- Diagnosis in an emergency in some cases of suspected meningitis and encephalitis;
- Studies of blood products within CSF following suspected subarachnoid haemorrhage (on occasion);
- Measurement of CSF pressure, e.g. idiopathic intracranial hypertension;
- Removal of CSF therapeutically, e.g. idiopathic intracranial hypertension;
- As an aid to diagnosis by assay of CSF constituents in various neurological conditions, e.g. MS, neurosyphilis, sarcoidosis, Behçet's disease, chronic infection, neoplastic meningeal involvement, polyneuropathy and some cases of dementia; and
- Intrathecal injection of contrast media and drugs.

In suspected CNS infection, meticulous attention should focus on examination for cells, cell types and microbiological tests. Close liaison between clinician and microbiology laboratory is essential. In addition to cell counts on fresh CSF, bacterial stains (Gram, Ziehl–Neelson), stains for fungi (India ink and others) and specific microbiological techniques (e.g. polymerase chain reactions for bacterial antigens, syphilis serology) are invaluable. Repeated CSF examination may be necessary in the diagnosis of chronic infections such as TB.

Clinical and laboratory procedures for CSF spectrophotometry (e.g. rapid transport of specimens) should be clearly established if estimations of CSF methaemoglobin and bilirubin are to be made following suspected subarachnoid haemorrhage. For any specific CSF test, such as oligoclonal band (OCB) and immunoglobulin G (IgG) estimations, requests should be clearly stated with the initial CSF specimens. Parallel blood samples (e.g. sugar, OCB) should be taken, when these are appropriate.

Informed consent, risks of LP, CSF removal and intrathecal drugs

The LP procedure should be explained to the patient and its potentially painful nature. Written consent should be sought and if at all possible obtained.

The principal risks of LP relate first to the removal of CSF. This changes the relatively steady state pressure relationships within the brain and spinal cord. Coning (see below) can occur. CSF often continues to leak through the puncture site in the lumbar dura. This commonly leads to low pressure (low volume) headaches (Chapter 11) and exceptionally to intracranial subdural haematoma.

Secondly, there are local complications at the site of LP:

- Local infection and meningitis;
- Trauma – local pain, nerve root damage;
- Bleeding;
- Spinal epidural haematoma; and
- Arachnoiditis (see Chapter 15).

Inappropriate intrathecal injection of drugs, e.g. antibiotics and cytotoxics, is also well-recorded, sometimes with fatal consequences. Such tragedies are typically a product of inexperience. LP should not be performed without clear risk appraisal in any event, especially in the presence of raised intracranial pressure.

Contraindications to lumbar puncture

- Suspicion of a mass lesion within the brain or spinal cord. Caudal herniation of the unci and cerebellar tonsils (coning) may occur if an intracranial mass is present and the pressure below is reduced by removal of CSF. Spinal cord compression may worsen (or even develop) if an unsuspected cord tumour is present. Such well-recorded but unusual complications can develop within minutes of lumbar CSF being withdrawn.
- Any cause of suspected raised intracranial pressure, without careful consideration;
- Local infection near the LP site;
- Congenital abnormalities in the lumbosacral region (e.g. meningo-myelocoele);
- Platelet count below 40×10^9/L and other clotting abnormalities, including anticoagulant drugs.

Unconscious patients and those with papilloedema must have CT or brain MRI before LP. These contraindications are relative: there are circumstances when LP is carried out despite them, e.g. clinically secure diagnosis of benign intracranial hypertension. The issue of unsuspected low cerebellar tonsils, that may descend further through the foramen magnum following lumbar CSF removal, may in future dictate that before LP, a brain MRI will be required, except in an emergency.

LP technique

The patient is placed on the edge of a bed or trolley in the left lateral position with knees and chin as close together as possible. The spine should be as horizontal as possible. An experienced assistant is invaluable. Several pillows are useful to help with the patient's alignment and comfort.

The third and fourth lumbar spines are felt and marked. The fourth lumbar spine usually lies on a line joining the iliac crests.

Using sterile precautions, 2% lidocaine (lignocaine) is injected into the dermis, raising a bleb in the skin of either third or fourth lumbar interspace. Deeper injection of local anaesthetic should follow. The LP needle (22 gauge atraumatic disposable) is pushed through the skin in the midline. The needle is pressed steadily forwards, slowly and slightly towards the head, the operator feeling with the needle tip for the spinal interspace, pausing and/or re-aiming the needle if local resistance is encountered or substantial pain provoked. In difficult cases, radiological help may be necessary and LP carried out under screening control. When the LP needle tip is felt to penetrate the tense dura mater, the stylet is withdrawn and a few drops of CSF allowed to flow.

The CSF pressure is then measured by connecting a manometer to the shaft of the needle. Normal pressure is 60–150 mm of CSF. The CSF fluid level in the manometer oscillates slowly with respiration and transiently with the pulse and rises briefly on coughing or gentle pressure on the abdomen, assuming the bore of the needle is freely patent. CSF specimens are collected in three sterile containers. An additional fluoride sample for CSF sugar level, with a simultaneous blood sample, should be taken when relevant (e.g. in meningitis). CSF 5–15 ml is usually removed for diagnostic purposes. The tests carried out routinely are shown in Table 3.13.

CSF pressure and naked-eye appearance should be recorded in the notes: i.e. clear, cloudy, colourless, yellow (xanthochromic), red – and if red, whether or not the colour begins to clear after the first or subsequent sample. Patients are asked to lie flat after LP to avoid subsequent headaches, and to drink plenty, manoeuvres of uncertain value. Analgesics may be needed for post-LP headaches and occasionally treatments for prolonged low pressure headaches, e.g. epidural autologous blood patches (see Chapter 11). Post LP headaches often last several days but may continue for weeks or occasionally for longer periods.

Biopsy of brain, muscle and peripheral nerves

One of the difficulties in neurology compared with other clinical specialities is that CNS tissue is less accessible to biopsy than, for example, the liver, lung or intestinal mucosa. All biopsies in neurology require specialized techniques, involve risk and careful attention to detail – for collection of specimens, transport and processing. The detailed assessment of biopsies of muscle, nerve, brain and meninges are not considered here, but some general observations are helpful.

Biopsy of brain or of brain lesions, with or without meningeal biopsy, is carried regularly for diagnosis of brain tumours, for other mass lesions and other specific indications. Stereotactic procedures are employed increasingly (Chapter 20). If there is any question of an infective process, specimens for microbiological study should be collected in appropriate media with close liaison between operating theatre and laboratory. Brain biopsy is also of some value in diagnosing dementia and for rarities such as Rasmussen's disease, Whipple's disease or vasculitis. Biopsy should where possible be directed at structurally abnormal tissue, seen on imaging. 'Blind' biopsy of 'MRI-normal' brain has a low diagnostic yield. Meningeal biopsy is sometimes valuable in the diagnosis of chronic infection or inflammatory diseases, e.g. sarcoidosis. The principal risks are those of infection, haemorrhage or damage to the surrounding brain. However, in competent hands, morbidity is well below 2%.

Peripheral nerve biopsy (sural or radial) is commonly performed in the diagnosis of chronic neuropathies. The risks are few: infection is rare but painful paraesthesiae sometimes follow in the distribution of the nerve fascicles removed. A numb patch on the lateral aspect of the dorsum of the foot is to be expected following sural nerve biopsy and following radial nerve biopsy at the wrist, a patch (usually trivial) in the snuff box. Detailed microscopical studies are carried out, including electron microscopy. While many nerve biopsies do not alter management, any misgivings are brought roundly into focus by finding unexpected steroid-responsive chronic inflammatory demyelinating polyradiculoneuropathy (Chapter 9) or the occasional diagnosis of leprosy.

Muscle biopsy (deltoid or quadriceps) is a standard procedure for cases of inflammatory muscle disease, dystrophies, mitochondrial disease and metabolic myopathy with appropriate specialized stains and biochemical assays. All muscle biopsies should be processed by specialized laboratories with ready access to electron microscopy. Opinions have varied about the yield of open muscle biopsy or needle biopsy; open biopsy is now usual in most neurology units.

Neuropsychological testing

The Mini Mental State Examination and Cognitive Screening Tests are mentioned above. More detailed testing and recording

Table 3.13 Normal cerebrospinal fluid (CSF) appearance and constituents.

Observation/measurement		Comment
Appearance	Crystal clear, colourless	Normal CSF is crystal (gin) clear when held to the light
Pressure	60–150 mm of CSF with patient recumbent	Patient must be relaxed and needle patent to see lumbar CSF rise and fall in manometer
Cell count	<5/mm^3. *No* polys: mononuclears only	*One* polymorph/mm^3 *just* acceptable
Protein	0.2–0.4 g/L	Slightly raised protein <0.7 g/L rarely pathological
Glucose	$^2/_3$ to $^1/_2$ of blood glucose	CSF glucose <$^1/_2$ blood glucose suspicious
Culture	Sterile	Do not accept contaminants
IgG	<15% of total CSF protein	Usually only on request
Oligoclonal bands	Absent	Parallel blood sample

definitive deficits in cognition are of great value in clinical neurology. However, in no area of investigation is there more variation in reporting, nor in the scope of testing. In part, this is because of the various disciplines within which neuropsychology finds a place of importance – in neurology, in psychiatry and within many aspects of human behaviour. The tests performed are often complex, highly specialized and their precise details outside the knowledge of a general neurologist. Neuropsychological reports tend to vary in emphasis – some dwelling on perceived psychiatric diagnoses, others on treatment, while others – more within the ambit of daily clinical neurology – purely upon cognitive function. It is in the latter field that neurologists find most value. Cognition is, after all, the unique function of the human brain (Chapter 7).

Intellectual function overall

The Wechsler Adult Intelligence Scale-Revised (WAIS-R) is divided into subtests. The Verbal IQ with the National Adult Reading Test (NART) provides a measure of the premorbid optimal level of function. Performance IQ gives a measure of present overall cognitive ability.

Memory

Many tests to investigate different aspects of episodic memory are available:

- The Paired Associate Learning Test studies verbal memory;
- Story Recall addresses sequencing and importance of items within an incident;
- The Topographical Recognition Memory Test and Rey Figure Tests assess awareness and recall of spatial issues; and
- The Recognition Memory Test is available in Verbal and Visual versions.

Tests for verbal and non-verbal memory are useful in the localisation of damage to either the dominant or non-dominant temporal lobe, for instance in the work-up for possible epilepsy surgery.

Language

Spontaneous speech is assessed for fluency, articulation, prosody and nominal impairment. The Graded-Difficulty Naming Test measures nominal ability.

Literacy and calculation

Reading, spelling and calculation are assessed, for both speed and efficiency. The Graded-Difficulty Spelling and Graded-Difficulty Calculation Tests record the levels of attainment achieved.

Perceptual function

Many tests focusing upon perceptual tasks are available. Silhouettes, Object Decision and Incomplete Letters (usually incomplete large capitals E, N and K) address visual perception. The Number Location Tests and the Visual Object and Space Perception (VOSP) battery study spatial perception.

Frontal and executive function

Tests address the ability to solve problems and test judgement; unfortunately many frontal function tests are less reliable than one would wish for distinguishing whether or not a problem has an organic substrate. The Wisconsin Card Sorting Test is often used, testing the ability to display flexibility and choice in the face of challenges. After seeing a number of stimulus cards, the participant is given additional cards and asked to match each to a stimulus card – and not informed whether one match is correct before progressing to the next.

The Hayling Sentence Completion Test consists of two sets of 15 sentences apiece, each with the last word missing. A sentence is read aloud; the participant has to complete it.

The Behavioural Assessment of Dysexecutive Syndrome (BADS) is a battery of six tests and also questionnaires that require planning, initiation, monitoring and behaviour adjustment to various demands:

1. Rule Shift Cards (testing perseveration);
2. Action Programme (practical problems, e.g. extracting a cork from a narrow tube);
3. Key Search (finding a lost key in a field);
4. Temporal Judgement (judgement/abstract thinking, e.g. a dog's life expectancy);
5. Zoo Map (formulation/implementation of plans); and
6. Modified Six Elements (ability to time-manage).

Attention

Various tests of attention are used. Counting the number of letters A in a patchwork of letters is one of the simplest. Other named Tests of Everyday Attention (TEA) include Elevator Counting, Elevator Counting with Distraction, Telephone Search with and without Distraction.

Formulation and conclusions

The formulation carried out by the neuropsychologist draws together the results. It is vital that problems with concentration and attention are given appropriate weighting, especially when other clinical issues such as pain, clinical depression and anxiety related to illness are present. The neurologist needs to know above all whether non-organic factors might have influenced the test results. Thus, close liaison between neurologist and individual psychologist is important.

Terminology, or grammar of clinical neurology

Names for patterns of symptoms and signs can be called the vocabulary or grammar of clinical neurology – terms and phrases we use to describe and encapsulate particular conditions. The most common complaints worldwide, such as headaches, vertigo, dizziness, infections and recognizable neuromuscular disease and cognitive impairment, are dealt with in specific chapters. This is a brief overview of some important patterns seen in clinical practice.

Focal cortical disorders

The cortical mantle is exceeding highly developed and differentiated in humans. Dementia, i.e. global cognitive impairment, with its various causes and particular modular features that frequently involve episodic memory and other specific aspects of cognition, is by far the most common cortical problem (Chapter 7). This section outlines briefly features of the principal focal cortical lesions:

- Language disorders;
- Non-dominant hemisphere lesions;
- Frontal, temporal, parietal and occipital lesions.

While precise cortical mapping by clinical assessment has largely been superseded by imaging, an understanding of the variation between individual brains and a general working knowledge of the cortex is essential. This section summarizes some basic clinical aspects within this field, but the reader should be aware of its complexity, the wide variation in approach between the disciplines of neurology, neuropsychiatry and psychology. Many brain functions are not strictly localised: beware theories that appear simplistic, highly specific or didactic.

Language and its disorders

Within a cultural group, language is that combination of sounds or writing with symbolic meaning necessary for interactive communication. A phoneme is the shortest unit of language. A phoneme may have a different meaning in different languages. What sounds like 'we' (the pronoun) in English will sound like 'oui' [yes] to a person speaking French. Some phonemes have become almost universal, e.g. OK.

- Aphasia (*syn.* dysphasia) describes disorders of spoken language.
- Agraphia (*syn.* dysgraphia) describes disorders of written language.
- Acquired alexia (*syn.* dyslexia) is a disturbance of acquired reading ability.
- Dysarthria is disordered oral speech production (articulation).
- Dysphonia is abnormality of the noises made by passage of expired air over poorly vibrating or paralysed vocal cords.

Aphasia, strictly speaking, means complete loss of language function; dysphasia means a disorder of language function. The prefixes dys- and a-, for aphasia and these related communication problems, are used interchangeably in this section, as they are in practice.

The study of cerebral localization can be said to have commenced with recognition in the 19th century that the left hemisphere was the seat of language function in the majority of humans. In 1861, Paul Broca (1824–1880), professor of surgical pathology in Paris, described non-fluent (expressive) aphasia in a patient with a tumour in the left third frontal convolution. In 1873, Dr Carl Wernicke (1848–1905), who had qualified in Breslau just 3 years earlier, described fluent jargon aphasia (speaking unintelligible words) in a patient with a lesion more posteriorly placed, in the angular gyrus. Classic concepts, postulating the system overall, e.g. those of Lichtheim (Dr Ludwig Lichtheim, Breslau, 1845–1928) remain useful. To summarize these, first there are cortical modules for conceptual meanings, connected by transcortical pathways to a posterior (temporal) centre for processing phonemes. Secondly, via the arcuate fasciculus, language information passes to an anterior (frontal) centre for programming and delivering speech output.

Difficulty naming objects – nominal aphasia – soon became established as a screening test, or lowest common denominator for lesions over a wide area of the posterior frontal, temporal and lower parietal regions of the dominant hemisphere. Word retrieval in nominal aphasia correlates with frequency of a word in everyday life. Thus, slightly unusual objects, e.g. the winder button (stem button) rather than the wristwatch itself are preferable when asking the question: 'What is this called?'

This section summarizes features of four basic varieties of aphasia. Everyone finds the terminology difficult when more unusual and complex forms of aphasia are described. Mixed and incomplete varieties of aphasia are common.

Non-fluent aphasia (Broca's aphasia, motor or anterior aphasia)

This is the most common variety of aphasia following stroke. The hallmark is the slow, incomplete and laboured production of language, with a major breakdown of grammatical output:

- The patient is fully aware of the problem and often distressed.
- Nouns, more than conjunctions and adjectives are retrieved. Grammar and syntax are lost. Tenses of verbs are frequently incorrect.
- Perseveration is common.
- Prosody (normal rhythm) is lost.
- The ability to repeat phrases is lost.
- Comprehension is relatively preserved but complex multiple commands usually reveal some lack of understanding.

The lesion is around the left, third (inferior) frontal convolution, lower (inferior) motor cortex and nearby temporal insula. The closeness of the motor strip to Broca's area explains why contralateral UMN facial weakness and hemiparesis (or hemiplegia) are frequently seen. There may also be facial apraxia – dissociation between the idea and production of a non-verbal facial movement such as whistling. Cortical dysarthria describes the situation when this apraxia extends to speech itself, causing slurring and hesitancy.

Fluent aphasia (posterior, sensory or Wernicke's aphasia)

The essence of this variety of aphasia is the production of fluent speech with language that lacks meaning. Patients often appear to have little insight into an evident problem and are talkative. They may look bewildered and are sometimes agitated. Phonemic and semantic confusions are common and sometimes so prominent that neologisms (new, meaningless words) are formed with excessive outpourings of meaningless fluent jargon. Prosody tends to remain normal. The ability to repeat phrases is lost; comprehension is lost.

These cases are sometimes mistaken for a form of psychosis or psychiatric illness. If a patient with Wernicke's aphasia recovers (which is unusual), they say they were unaware they were speaking rubbish and that they could not grasp what others were saying to them, as if listening to an incomprehensible language.

Conduction aphasia

Reduced ability to repeat spoken words or phrases but with reasonable comprehension are hallmarks of conduction aphasia, seen with a lesion of the arcuate bundle between posterior and anterior language areas (and other posteriorly situated lesions in the cortical language area). The pattern consists of:

- Fluent speech, with nominal dysphasia and semantic confusions;
- Poor repetiton;
- Relatively preserved comprehension.

Trancortical aphasias, motor and sensory

Preserved ability to repeat spoken words, phrases and sometimes longer passages defines transcortical aphasias. The arcuate fasciculus remains intact. Transcortical motor aphasia (TMA) describes a non-fluent aphasia caused typically by a lesion in the left anterior superior frontal region. Patients with TMA have halting and effortful spontaneous speech, with phrases typically of only one or two words. However, they retain the ability to repeat words, phrases or sentences. Repetition is believed to be preserved because the arcuate fasciculus remains intact. Comprehension remains reasonably normal.

Transcortical sensory aphasia (TSA) is caused typically by lesions behind Wernicke's area in the temporal–occipital–parietal region. TSA patients have poor comprehension but with fluent and reasonably grammatical speech, with preserved repetition. However, they tend to have semantic paraphasia, i.e. they do not use words that are correct, but substitute words of similar content, e.g. pear for apple, pen for writing paper.

Mixed transcortical aphasia (MTA) is characterized by both severely reduced language output and by impairment of comprehension, but with preservation of the ability to repeat words and phrases. Patients with this unusual form of transcortical aphasia have a major disability, with difficulty producing propositional language and understanding what is being said to them. However, they can repeat phrases and even long complex sentences, and finish a familiar poem or song, once they hear the beginning of the composition. Generally, in MTA, both Broca's and Wernicke's areas remain intact, and the arcuate fasciculus between them remains intact. The surrounding regions are believed to be damaged, isolating these areas.

Agraphia and acquired dyslexia

Written symbol comprehension is perceived in the region of the dominant angular gyrus. Lesions in this cortical region cause acquired alexia usually with agraphia and posterior aphasia. Isolated alexia without agraphia is seen with either anterior occipital lobe lesions and/or lesions of the splenium of the corpus callosum.

Temporal lobe lesions

Many small (<2 cm) unilateral temporal lobe lesions are silent in terms of cognitive abnormalities. Epilepsy is common (Chapter 6). Upper quantrantic hemianopia is seen when the forward-looping fibres (Meyer's loop, Chapter 2) are damaged.

A lesion in the dominant anterior temporal lobe extending more than 6 cm from the anterior pole often causes a posterior aphasia. Non-dominant anterior temporal lobe lesions are sometimes associated with inability to recognize faces (proposagnosia). Unilateral mesial temporal lobe lesions can also produce subtle changes in memory, often silent clinically until revealed by specific neuropsychological tests.

Bilateral temporal lobe lesions (e.g. following herpes simplex encephalitis) cause profound loss of memory for recent events. Bilateral temporal lobe injury in primates causes hypersexuality, hyperactivity and aggressive behaviour (Klüver–Bucy syndrome). Sometimes, in humans, there are elements of this (episodic temper dyscontrol) but the usual outcome is aimlessness, diminished libido and impaired potency.

Frontal lobe lesions

As in the temporal lobes, many small frontal lesions remain silent. Some (see above) cause anterior aphasia. Substantial damage (e.g. traumatic frontal brain injury, direct or contra-coup) causes a highly disabling lack of social control. Examples of this are:

- Abandonment of the usual social inhibitions – from somewhat inopportune, often rude 'frontal' comments to profound disturbances such as urination, exposure or masturbation in public.
- Inappropriate jollity (witzelsucht) – jokes and tales often overlong and unwanted.
- Apathy, lack of initiative and poor planning (dysexecutive problems).
- Irritability, anger, distractability, inappropriate placidity in the face of irritation or obsessional behaviour.
- Continuing one action when another is appropriate – motor perseveration.
- Utilization behaviour. The subject sees something, typically a tool – a tendon hammer or a stethoscope during a consultation – and begins to use it.

These frontal lobe features may be accompanied by a grasp reflex, sucking, pout and palmo-mental reflexes. Deep bilateral frontal lesions, e.g. small vessel disease in the elderly, can lead additionally to gait apraxia and failure to initiate walking (gait ignition failure), often with sphincter disturbance.

Frontal behaviour of lesser degrees has become a common plea in claims following minor head injury, trivial loss of consciousness and normal brain imaging. The patient and relatives are asked about features such as impulsivity, temper, socialization, fiscal ability, multi-tasking, planning, prioritization, depression and anxiety – common problems for many in stressful situations. There is a distinct lack of evidence that these complaints are caused by brain injury following a minor blow to the head.

Frontal lobe seizures are described in Chapter 6.

Occipital lobe lesions

Field defects of occipital lobe lesions are mentioned in Chapter 13. Neglect or even denial of virtually complete visual loss (Anton's syndrome) are sometimes seen following bilateral occipital lobe infarction. An explanation for 'blind sight' is provided by the preservation of the anterior visual pathways to the lateral geniculate bodies that are below the level of awareness. Epilepsy, with episodes of flashing lights or, rarely, more formed features, can occur with lesions in occipital lobes.

Parietal lobe lesions

These areas are concerned with the integration into perception of complex visual and somatosensory information – the awareness of body parts in space and their relation to objects. This has led to a complex nomenclature to describe many varieties of perceptual defect. Attempts to associate precise areas of the parietal lobes to particular functions or syndromes are bedevilled by variation between individuals, an indication that the brain is not divided into compartments in the way many classic texts described. The following are seen regularly with lesions of either parietal lobe:

- Attention defects in the contralateral visual field and neglect of the opposite side of the body. Lower quadrantic homonymous field defects occur when the optic radiation is damaged.
- Astereognosis – inability to recognize common objects placed in the contralateral palm despite apparently normal sensation or figures drawn there simply with the examiner's finger.
- Pseudo-athetosis and/or drift of an outstretched contralateral hand.

Sensory epilepsy is sometimes a feature of parietal lobe lesions.

Dominant parietal lesions

Inability to execute a skilled movement despite no discernable weakness may be seen – ideomotor apraxia. For example, the patient does not respond to verbal suggestions such as 'Imitate combing your hair' or 'Pretend to turn a key in a lock'. Typically, they are bewildered, moving the hand in a non-purposive way.

Gerstmann (Professor Josef Gerstmann, 1857–1940) described:

1 Right–left disorientation;
2 Inability to name each finger (little, ring, middle, index) – known as finger agnosia;
3 Inability to calculate; and
4 Dysgraphia in cases with dominant parietal lobe lesions.

Gerstmann's syndrome (1 + 2 + 3 + 4) is rare and may reflect the chance association of these parietal features.

Neglect of contralateral limbs is typically less prominent with dominant than non-dominant parietal lesions.

Non-dominant parietal lesions

Neglect of the opposite limbs and inability to comprehend spatial arrangements leads to patients becoming lost in familiar surroundings, to muddled dressing (dressing apraxia) and to constructional apraxia – inability to construct or draw shapes such as a house or a clock face. The left side of a picture drawn or described (e.g. numbers 1–5 on a clock face) will tend to be omitted by a right-handed patient with a right parietal lesion. Inability to recognize familiar faces (proposagnosia, see also temporal lobes) may occur – especially distressing for close relatives if this extends to themselves. Neglect of the contralateral limbs can extend to denial that the limbs are the patient's own.

Motor system abnormalities of the brain and spinal cord

The patterns of abnormality within the motor system are both distinct and recognizable – and the classes of disorder relatively few. Features of hemiparesis (and hemiplegia) and paraparesis, cerebellar syndromes and disorders of movement are summarized here.

Hemiparesis

Weakness of the limbs of one side resulting from a pyramidal tract lesion is known as hemiparesis, the term paresis indicating that weakness is not total – cf. hemiplegia, total loss of power following a stroke. The earliest physical signs of an early hemiparesis, sometimes before weakness becomes evident are scuffing of the toe of one shoe, drift of one outstretched upper limb and a trace of impaired fine finger and/or toe movement. Thereafter emerge the five principal features of a pyramidal lesion:

1 Increase in tone;
2 Weakness in a typical pattern (upper limb extensors weaker than flexors; lower limb flexors weaker than extensors);
3 Progressive loss of fine movement;
4 Unilaterally exaggerated reflexes; and
5 Extensor plantar response (Babinski) and absent abdominal reflexes.

These features gradually develop as a hemiparesis progresses or emerge following hemiplegia after a stroke. However, in either case there may not be a full house of these five abnormalities – to use the poker hand analogy. Not all these features of a UMN lesion are required to make a firm diagnosis.

As a corollary, to find weakness alone as the only feature of a hemiparesis is highly unusual and raises the question of whether or not the problem has an organic basis.

Cerebellar syndromes

Features of cerebellar disease are well-defined and straightforward to recognize compared to our knowledge of the complexity of cerebellar function (Table 3.14). The need to perform examination correctly to elicit early signs is emphasized.

In established cerebellar disease there are several important practical points. The first relates to clinical urgency. If an expanding mass lesion of the cerebellum is strongly suspected or found on imaging, there needs to be speedy liaison with a neurosurgeon. While all mass lesions of the brain are potentially serious, many cases of cerebral tumour above the tentorium can be dealt with in a somewhat routine expectant manner. With cerebellar tumours the rapidity of decline and development of tonsillar herniation over several hours can catch out the unwary.

Table 3.14 Principal features of cerebellar syndromes.

Lateral cerebellar lobe lesions
Rebound
Action tremor
Past-pointing
Dysdiadochokinesis
Dysarthria
Nystagmus (usually towards side of lesion) occurs if vestibular connexions are involved
Vermis lesions
Ataxia of stance, trunk and gait, sometimes with negative Romberg test (a test primarily of proprioception)

Table 3.15 Principal disorders of movement.

Akinetic-rigid syndromes
Idiopathic Parkinson's disease
Parkinsonism-plus
Drug-induced parkinsonism (e.g. phenothiazines)
Post-encephalitic parkinsonism
MPTP-induced parkinsonism
Childhood akinetic-rigid syndromes
Dyskinesias
Tremors
Chorea
Hemiballismus
Myoclonus
Tics
Dystonias
Paroxysmal dyskinesias
Drug-induced dyskinesias

MPTP: 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine,

Secondly, when a severe cerebellar syndrome is part of a multisystem degenerative processes, pyramidal features can be masked. Extensor plantars may be the only pyramidal sign. Finally, ascribing the ataxia of stance and gait of midline cerebellar lesions to non-organic causes has happened all too frequently. The many causes of cerebellar syndromes are discussed in Chapter 16.

Disorders of movement

The broad distinction between akinetic-rigid syndromes and dyskinesias is valuable. The principal disorders are summarized in Table 3.15 and discussed in more detail in Chapter 5. No amount of written description can surpass looking at movements, either in the flesh or on video.

Some presentations of movement disorders cause diagnostic difficulties regularly. First, when an akinetic-rigid condition becomes apparent, early idiopathic Parkinson's disease tends to be over-diagnosed and treated. The reality, which becomes evident some years later, is that the diagnosis is another, less common akinetic-rigid syndrome. Parkinson's disease (PD) is almost always obviously asymmetrical and should also be diagnosed with caution if rest tremor is not apparent. Progressive supranuclear palsy or multiple systems atrophy tend to be symmetrical from the onset, although the poverty of movement is similar to that seen in PD. Early Wilson's disease should always be considered in a akinetic-rigid syndrome with unusual tremor developing below the age of 40.

Benign essential tremor (BET) can cause difficulty. Usually in BET, tremor is seen when the limbs adopt a particular posture. However, there are forms of BET that mimic benign tremulous PD in the early stages. To complicate matters, occasionally action tremor is seen in BET, raising the possibility of cerebellar degeneration. The passage of time and keeping an open mind about the diagnosis for some months or longer usually sort out these difficulties.

Early chorea is also easy to miss, being mistaken for restlessness and normal fidgeting. A minor degree of dystonia can also escape recognition. Lower limb myoclonus can look remarkably like the ankle clonus of spasticity.

Finally, the diagnosis of a psychologically determined movement disorder is fraught with difficulty, and frequently turns out in time to be wrong when it is made early in the course of a condition. In movement disorder clinics, a substantial proportion of those originally labelled as functional, somatoform or diagnosed as conversion hysteria (whichever term is chosen) turn out in time to have organic disease.

Paraparesis

Spastic paraparesis – weakness of the lower limbs of cord or rarely, cortical origin – is one of the pivotal diagnoses of clinical neurology. Prior to the era of MRI, clinical examination had a vital role in differentiating between cord compression, a potential neurosurgical emergency, and the medical causes of paraparesis.

As with a hemiparesis, the clinical picture begins with subtle features:

- Scuffing the toes of shoes, often worse on one side;
- Stiffening of gait, but with retention of a narrow base;
- Noticeable beats of ankle clonus, e.g. on a step or kerbstone;
- Changes in lower limb sensation.

When cord compression is the cause, e.g. with a slowly growing thoracic meningioma, pain at the site of compression is associated with increasing weakness, spasticity and a sensory level, rising from below to the site of compression. The patient complains of numbness or altered sensation commencing in the feet that marches upwards gradually over weeks or months. Brown-Séquard features (pyramidal signs on one side, spino-thalamic on the other; see below and Chapter 2) may become apparent.

These features apply equally to tetraparesis (*syn.* quadriparesis).

The five principal features of a pyramidal lesion may not all be present. Pain may not be present in cord compression. The clinician must be wary and seek out subtle signs. Marked asymmetry can sometimes cause difficulty.

Two principal questions arise when spastic paraparesis is diagnosed clinically:

1 Is this caused by spinal cord compression?

2 Is this a result of one of the more common recognizable conditions in which paraparesis is part of the clinical picture?

- Multiple sclerosis
- Motor neurone disease
- Subacute combined degeneration of the cord
- Syringomyelia
- Parasagittal meningioma (rare).

Paraparesis is also caused by many other rarities – vascular anomalies of the cord, adrenoleucodystrophy, copper deficiency and lathyrism to mention four (see Spinal Cord Disorders, Chapter 15).

There can be many difficulties with the diagnosis of paraparesis, both in the process of referral to a neurologist and within the discipline of neurology itself. It is not helpful to write an exhaustive list of sources of error but several features are evident. The first issue is that in the community and in primary care, the emergence of difficulty walking is sometimes not taken seriously – and the early features of a paraparesis can pass unrecognized unless a physical examination is carried out. The onset of a disturbance of gait always demands an explanation.

A second issue within neurology is the misinterpretation of lower limb signs, thinking that they are pyramidal in origin when they are not. The following occur:

- Parkinson's disease affecting predominantly the lower limbs can be mistaken for spinal cord disease;
- Cortical myoclonus in the lower limbs can be mistaken for pyramidal ankle clonus;
- Stiffness of inflammatory muscle disease (e.g. polymyositis) with lower limb weakness can look like an emerging paraparesis;
- Brisk but normal lower limb reflexes are misinterpreted as pathological, thus prompting investigation for a paraparesis.

Brainstem syndromes

The complex anatomy of the brainstem is outlined in Chapter 2. Here, the features of some brainstem syndromes are drawn together, to encourage diagnosis by thinking in both vertical and dorso-ventral planes. Figure 3.6 is helpful as a schematic diagram. The hallmark of a typical brainstem syndrome is the coexistence of symptoms and signs of damage to motor and/or sensory fibres traversing the area vertically with damage to the cranial nerve nuclei of the brainstem. Syndromes involving oculomotor nerves III, IV and VI indicate upper or mid brainstem disease affecting the area dorsally. Mid and lower brainstem disease affects cranial nerve nuclei VII–XII.

Bulbar and pseudobulbar palsy are terms used to describe features of common lower brainstem syndromes (Chapter 12). Both cause dysarthria, dysphagia, drooling and respiratory problems. Bulbar palsy describes disease of the lower cranial nerves (IX, X, XII – nerves of the medullary bulb), their nuclei and the muscles these nerves supply. Pseudobulbar palsy is shorthand for UMN lesions of lower cranial nerve nuclei. MS, brainstem stroke and motor neurone disease cause pseudobulbar palsy, the latter usually both bulbar and pseudobulbar. Advanced PD and other extrapyramidal syndromes also cause poverty of movement of the bulbar muscles.

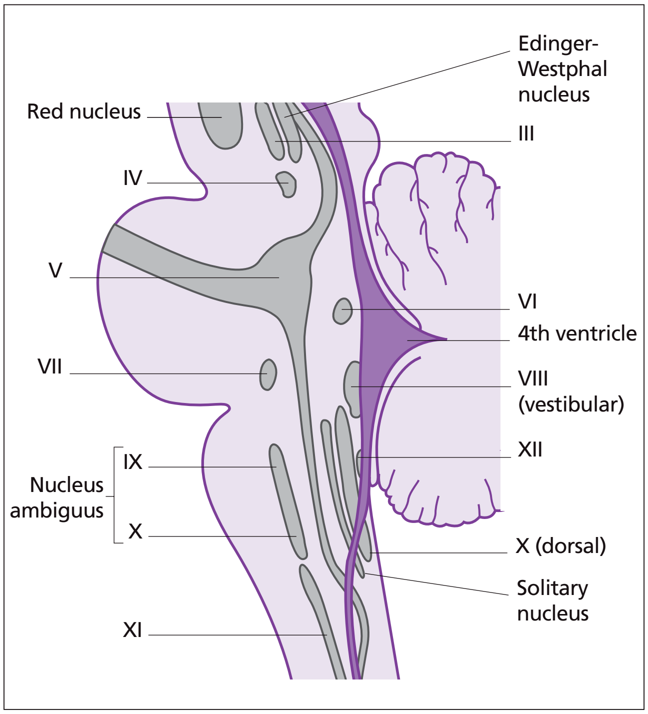


Figure 3.6 Brainstem: lateral schematic view. (From Hopkins 1993, with permission.)

Sensory abnormalities: patterns at different levels

Sensory symptoms and signs are difficult. The pattern of symptoms and their diagnostic meaning may be unfamiliar, examination time-consuming and its results less certain than the harder signs of reflex and motor abnormality. Eponyms, shorthand terms and phrases abound such as positive Tinel, tic douloureux, causalgia, anaesthesia dolorosa, lightning pains, Lhermitte, Brown-Séquard, dissociated sensory loss, suspended sensory loss, sacral sparing, thalamic pain and astereognosis. This section outlines the principal patterns of sensory disturbance seen in neurology.

An approach that some find valuable is to view sensory symptoms in one of two ways. First, if a sensory symptom is the principal complaint, such as the pain of trigeminal neuralgia (Chapter 12) or nocturnal tingling of the hands in early median nerve entrapment at the wrist (Chapter 9), its quality and distribution are frequently diagnostic. In other situations, the combination of the sensory history, sensory physical signs and additional neurological abnormalities on examination point to an anatomical diagnosis. An example is the use of sensory signs to determine a level of compression in the spinal cord when the principal feature is spastic paraparesis. Figure 3.7 summarizes various patterns of sensory loss at different levels.

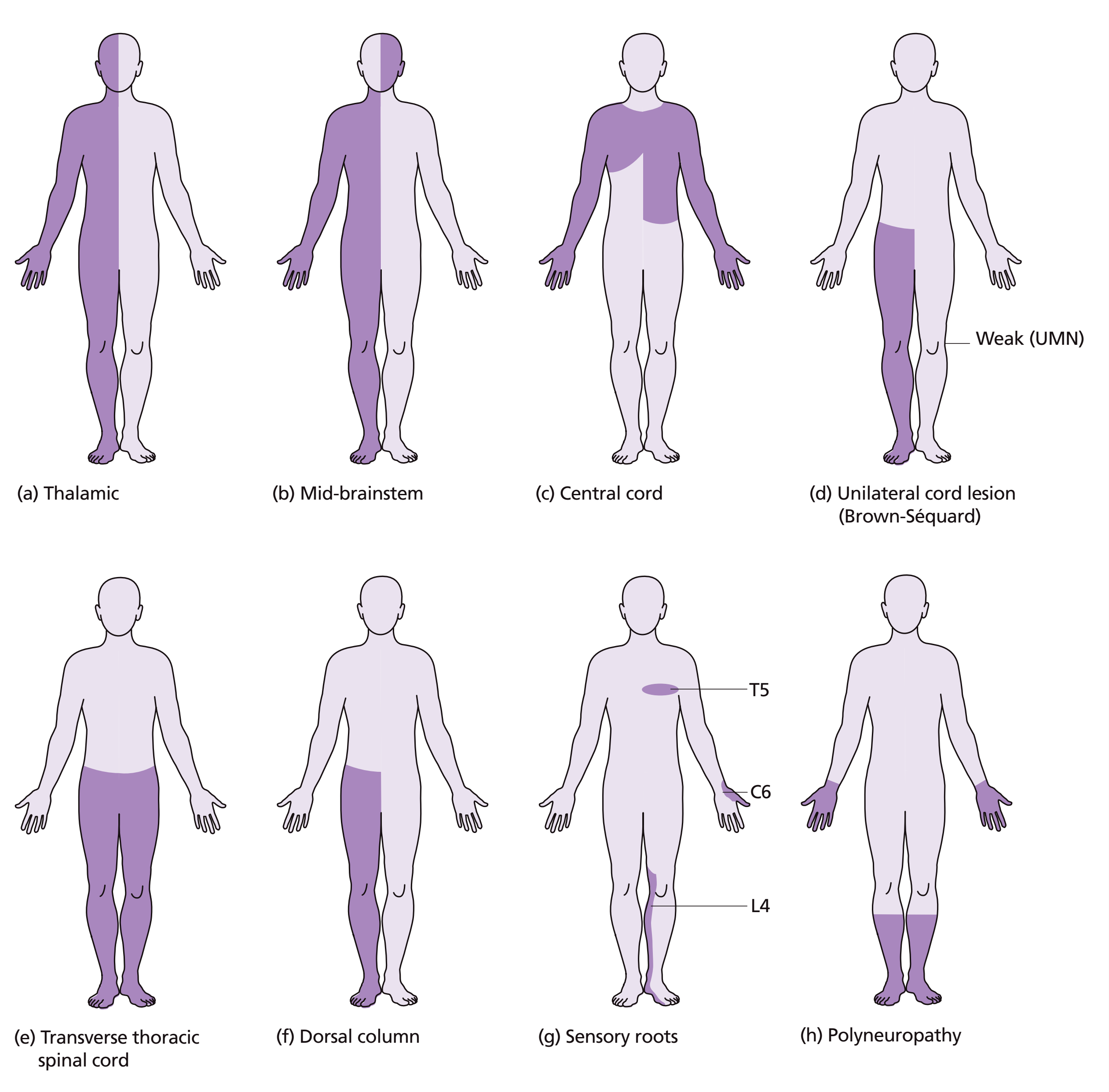

Weak (UMN)
(a) Thalamic
(b) Mid-brainstem
(c) Central cord
(d) Unilateral cord lesion (Brown-Séquard)
T5
C6
L4
(e) Transverse thoracic spinal cord
(f) Dorsal column
(g) Sensory roots
(h) Polyneuropathy

Figure 3.7 Principal patterns of loss of sensation.
(a) Thalamic lesion: sensory loss throughout opposite side (rare).
(b) Brainstem lesion (rare): contralateral sensory loss below face and ipsilateral loss on face.
(c) Central cord lesion, e.g. syrinx: 'suspended' areas of loss, often asymmetrical and 'dissociated', i.e. pain and temperature loss but light touch remaining intact.
(d) 'Hemisection' of cord or unilateral cord lesion = Brown-Séquard syndrome: contralateral spinothalamic (pain and temperature) loss with ipsilateral weakness and dorsal column loss below lesion.
(e) Transverse cord lesion: loss of all modalities below lesion.
(f) Isolated dorsal column lesion, e.g. demyelination: loss of proprioception, vibration and light touch.
(g) Individual sensory root lesions, e.g. C6 (cervical root compression), T5 (shingles), L4 (lumbar root compression).
(h) Polyneuropathy: distal sensory loss.
(From Clarke 2005, with permission.)

Sensory changes in peripheral nerve lesions

A lesion of an individual peripheral sensory nerve produces symptoms and signs within the distribution of the nerve. Nerve section is followed by complete sensory loss. Demarcation is clear-cut. The areas of sensory loss seen in individual sensory nerve lesions are discussed in Chapter 9. In nerve entrapment or partial damage, the quality of sensory disturbance varies between numbness, tingling and painful pins and needles. Dr Jules Tinel (1879–1952), the French neurologist, wrote about gunshot wound nerve injuries in 1916. He described painful tingling in the distribution of a damaged nerve when percussed – hence Tinel's sign, commonly positive when the median nerve at the wrist is tapped lightly, in cases of carpal tunnel syndrome.

Neuralgia (Chapter 22) describes pain of great severity in the distribution of a nerve or nerve root. In trigeminal neuralgia (tic douloreux, Chapter 12), the paroxysmal nature of the pain, its distribution and its electric shock-like quality is diagnostic.

Causalgia (complex regional pain syndrome type II, Chapter 22) describes chronic pain after nerve section or crush injury and is sometimes seen after amputation. Anaesthesia dolorosa is spontaneous pain occurring in an anaesthetic area. It is used to describe discomfort or chronic debilitating pain, developing for example after destructive procedures to the trigeminal nerve.

Sensory changes in polyneuropathy

Symmetrical, four limb, distal tingling, numbness or deadness are typical of polyneuropathy Sensory symptoms in the distribution of multiple individual nerves are seen in multiple mononeuropathy (Chapter 9).

Sensory root and root entry zone lesions

The distribution of spinal dermatomes is shown in Figure 3.8. Unlike peripheral nerves there is some overlap between adjacent

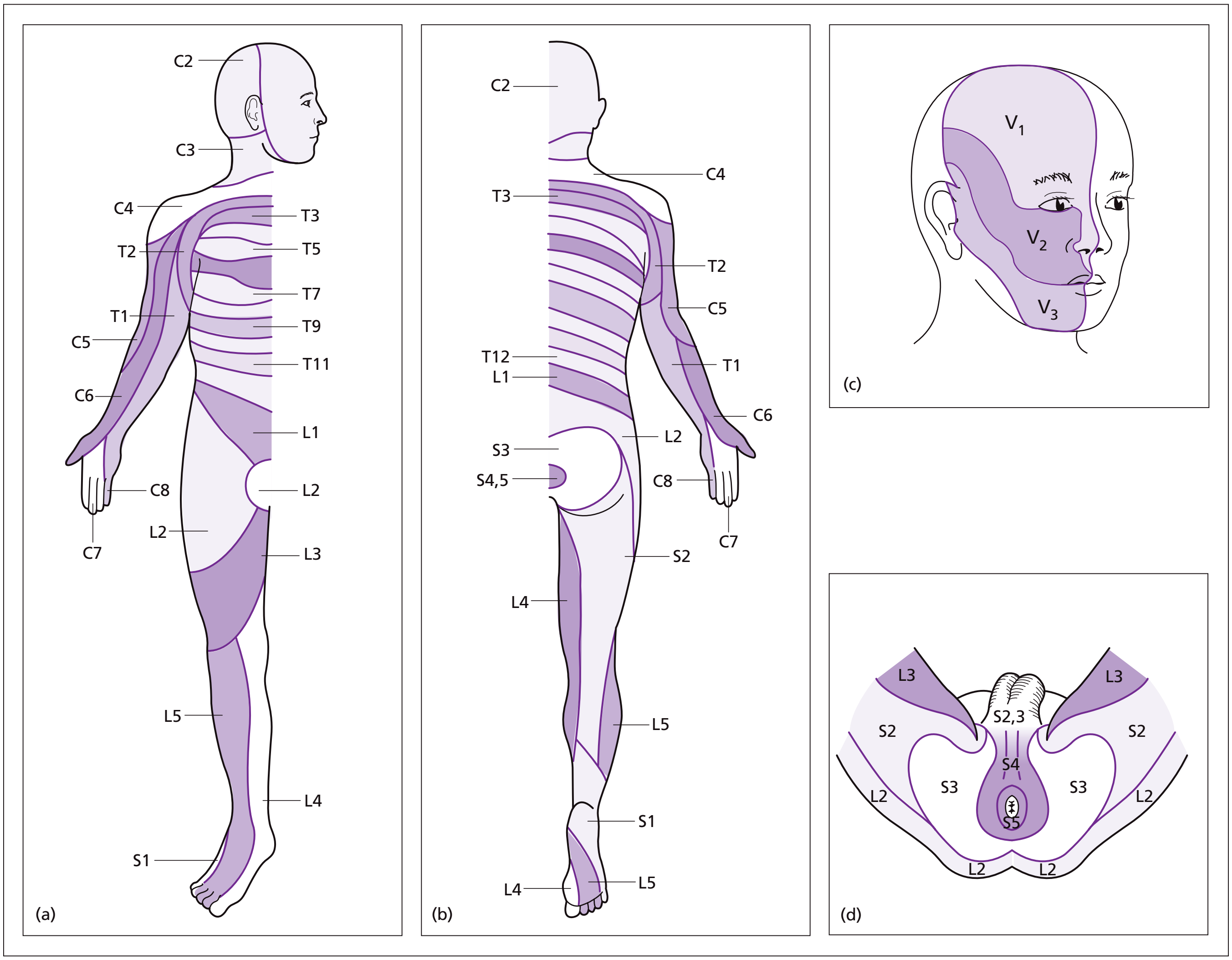


Figure 3.8 (a), (b) and (d) Spinal dermatomes. (From O'Brien 2000, with permission.) (c) Cutaneous distributions of divisions of Vth nerve. (From Patten 1996, with permission.) Precise distribution varies amongst published sources, especially for sacral dermatomes, perineum and Vth nerve.

dermatomes making the area of sensory loss following a single nerve root lesion smaller than shown. Root pain is typically perceived both within the dermatome and within the myotome (see below). It tends to be less well demarcated than pain seen in a peripheral nerve lesion. For example, with an S1 root lesion resulting from a lumbosacral disc, a sensory disturbance is felt down the back of the leg, typically without clear dermatome demarcation. Stretching of the nerve root (e.g. straight leg raising) or increasing local spinal CSF pressure (coughing, straining) typically makes matters worse.

When a root is affected within the cord, e.g. in tabes dorsalis, sudden, irregular, very intense stabbing pains involve one or more spots, typically on the ankle, calf, thigh or abdomen. These are known as the lightning pains of tabes and rarely seen today.

Neuralgia in the distribution of a nerve root can develop following shingles (post-herpetic neuralgia, Chapter 22). This is a persistent distressing burning pain.

Sensory changes in spinal cord lesions

Posterior columns

Symptoms, although they may be worse on one side, are often not clearly demarcated. Patients describe various patterns of symptoms:

- Band-like sensations around trunk or limbs;
- Limb clumsiness and deadness;
- Numbness and burning;
- Electric shock-like sensations.

Joint position sense, vibration, light touch and two-point discrimination become diminished below a cord lesion. Stamping gait and pseudochorea of the outstretched hands are the product of failing position sense.

Lhermitte's sign (strictly, a symptom) is a sudden electrical sensation down the back and into the limbs produced by bending the head forward, thus stretching the cervical cord. Lhermitte's is diagnostic of lesions of the posterior columns or occasionally caudal medulla. It is seen in:

- MS, typically in exacerbations
- Cervical myelopathy
- Radiation myelopathy
- Subacute combined degeneration of the cord (see below); and occasionally in
- Cord compression, Behçet's, Arnold–Chiari syndrome and following trauma.

This sensory phenomenon was first noted by Drs Marie and Chatelin (Paris, 1917); Dr Jean Lhermitte re-described it in 1920, writing the seminal article some 4 years later.

Spinothalamic tract lesions

A lesion within the spinothalamic tracts of the cord that causes conduction to fail produces changes in pain and temperature sensation below its level. With compression from outside the cord, e.g. by a thoracic spinal meningioma (extramedullary cord compression, see below), the sensory level will tend to rise, having commenced in the lower limbs until the level of the compression is reached as the tumour increases in size. This is because of the lamination of spinothalamic fibres in the cord. It is important to examine sensation with this in mind. Extramedullary cord compression is likely to affect both principal cord sensory pathways, i.e. both posterior column and spinothalamic. The patient may notice the loss of spinothalamic sensation, e.g. being unable to gauge the water temperature of a bath with their foot.

When a lesion is within the cord (intramedullary cord lesion, e.g. a syrinx – a central cavity) sensory loss can initially be confined to the spinothalamic pathways. Spinothalamic sensory loss is thus dissociated from other sensory modalities: the phrase 'dissociated' sensory loss implies that a syrinx or other central cord lesion is suspected. 'Suspended' sensory loss is a term describing another aspect also seen typically with a syrinx – a patch of dissociated sensory loss does not extend to the lower limbs and is thus 'hanging', usually on the thorax or abdomen.

'Sacral sparing' is another phrase used to capture the phenomenon of preserved sacral and perineal sensation when a central cord lesion expands centrifugally, damaging first centrally placed fibres and reaching last the spinothalamic sacral fibres on the periphery of the cord.

As a cavity develops within one half of the cord, the dissociated sensory loss on the opposite side becomes associated with pyramidal signs (e.g. a spastic lower limb) on the same side as the cortico-spinal pathway involved. This finding carries the eponym 'Brown-Séquard'. Dr Charles-Edouard Brown-Séquard (1817–1894) published a treatise in 1849 on the neurological effects of traumatic hemisection of cord. Originally from Mauritius, Brown-Séquard was a physician at the National Hospital. 'Brown-Séquard findings' imply spinothalamic signs on one side and pyramidal signs and dorsal column dysfunction on the other. They point to a lesion in one half of the cord, on the same side as the pyramidal and dorsal column loss. The patient may report: 'My left foot feels numb and cold and I can't feel the bathwater, but it's my right foot that drags.'

Sensory changes in brainstem lesions

Complex patterns of sensory loss occur with lesions in the brainstem, their character depending on the level of the lesion. Trigeminal sensory loss (Chapters 2 and 12) and dissociated (spinothalamic) sensory loss in the limbs (e.g. lateral medullary syndrome, Chapter 4) are seen. Usually, the sensory disturbance is part of a complex of physical signs and the site of the lesion determined more from the involvement of cranial nerve nuclei and brainstem connections than by the pattern of sensory loss.

Sensory changes following thalamic lesions

Destructive lesions of the complex thalamic nuclei and thalamocortical projections are relatively unusual causes of sensory symptoms in clinical practice. Two principal patterns are found. When the ventral posterior nucleus, lateral (VPL) and ventral posterior nucleus, medial (VPM) thalamic nuclei (Chapter 2) are damaged, e.g. following a thrombo-embolic stroke, contralateral hemi-anaesthesia develops immediately. All sensory modalities are usually affected. Sometimes, however, during the weeks or months following the stroke, as recovery ensues, highly unpleasant disabling persistent thalamic pain (post-stroke central pain, Chapter 22) develops in the partially anaesthetic limbs – usually as a permanent phenomenon. Such spontaneous pain does not develop following cortical lesions, nor following damage within the internal capsule or other basal ganglia nuclei outside the thalamus, but occasionally when the spinothalamic tract is damaged in the cord or brainstem.

Sensory changes in parietal lobe lesions

Features of parietal lobe lesions such as astereognosis, i.e. the inability to perceive the shape of an object, are mentioned earlier in this chapter. Focal sensory epilepsy, e.g. attacks of tingling or altered sensation, may be seen with parietal tumours. Of note, negative sensory symptoms, i.e. spontaneous distinct complaints of sensory loss, are unusual. It is more typical that a patient complains that a hand or limb 'doesn't work properly' or 'doesn't feel quite right'.

Mononeuropathy, polyneuropathy, root lesions

These notes summarize features of peripheral nervous system conditions, dealt with in detail in Chapters 9 and 12.

Mononeuropathy

Common isolated single nerve lesions (mononeuropathies) are distinct and easy to recognize once seen. Ulnar, median, radial, common peroneal (lateral popliteal), lateral cutaneous nerve of the thigh and sural nerve lesions are the most common. Most are caused by entrapment but there are other causes such as nerve tumours and vasculitis. Lesions of other peripheral nerves are relatively unusual. Cranial nerve lesions are discussed in Chapter 12.

Multiple mononeuropathy

This describes the occurrence of two or more such peripheral nerve lesions. The principal causes worldwide are leprosy, diabetes, hereditary neuropathy with liability to pressure palsies (HNPP) and various forms of vasculitis such as polyarteritis.

Polyneuropathy

Polyneuropathy (formerly known as peripheral neuropathy and polyneuritis) describes symmetrical conditions in which nerves die back – to cause combinations of peripheral sensory loss, muscle weakness and wasting with loss of tendon reflexes. It is frequently difficult to recognise clinically a neuropathy from its phenotype and to distinguish between genetic and acquired neuropathies.

Abnormal myelin appears more prone to inflammatory change than normal myelin: features of both genetic and inflammatory neuropathies can coexist.

Neurogenic muscle wasting

The crux of the matter is to distinguish between:
- Generalized muscle thinning – a normal finding in older age groups – and generalized loss of muscle bulk seen in cachexia;
- Widespread wasting seen in some myopathies, motor neurone disease and polyneuropathy;
- Focal wasting that follows denervation.

Focal neurogenic wasting is one hallmark of neurological disease. Neurological examination seeks out sites of predilection:
- Small hand muscles, supplied by ulnar and/or median nerves (T1);
- Guttering of the forearm flexors;
- Wasted anterior tibial compartment – sunken appearance lateral to the leading edge of the tibia;
- Wasted extensor digitorum brevis muscles – concave dished appearance of the small oyster-like muscles below each lateral malleolus.

Generalized thinning of muscles with advancing age is common and contributes to a gaunt appearance and spidery hands. However, the muscles are not weak on routine bedside testing. In pathological states, the muscles are weak. It is a reasonable approximation to say that muscles that are clinically normal (bulk, consistency and power) are almost always normal electrophysiologically and on biopsy.

Root lesions

The characteristics of a lesion affecting a nerve root are:
- Radicular pain;
- Wasting and weakness of affected muscles;
- Sensory loss or referred sensory symptoms; and
- Loss of or depression of one or more deep tendon reflexes.

Two descriptive terms are in common use. Radiculopathy is often applied to root lesions that are part of an inflammatory, vascular or neoplastic process, i.e. part of a disease, with derivative complex terms such as polyradiculomyelopathy. The phrase 'cervical or lumbar root problem' usually implies a compressive lesion, caused typically by degenerative disc and/or spinal disease. However, there is no real difference between the two; for simplicity the shorter English word, root, is preferred to the Latin *radix* to describe these common problems, but the more complex terms remain in widespread use.

Root pain or discomfort is caused by distortion or stretching of the meninges surrounding a nerve root and is perceived both in the myotome and the dermatome (Table 3.16). This clinical point is relevant in C7 root compression: pain is felt deep to the scapula (C7 muscles) and the sensory disturbance runs in the C7 dermatome to the middle finger. The triceps jerk is lost. For further discussion of root lesions see Chapters 9 and 15.

Cauda equina syndrome

The cauda equina ('horse's tail') describes the leash of nerve roots emanating from the lower end of the cord below vertebral body level L1/L2. Pressure (e.g. central L4/L5 disc) on the cauda equina

Table 3.16 Principal limb movements, nerve roots, muscles and peripheral nerves.

Movement	Root	Muscle	Peripheral nerve
Shoulder abduction	C5, (C6)	Deltoid	Axillary
Elbow flexion (supinated)	(C5), C6	Biceps	Musculocutaneous
Elbow flexion (mid-prone)	C5, (C6)	Brachioradialis	Radial
Wrist extension	(C6), C7, (C8)	Triceps	Radial
Tip of thumb flexion (and index finger flexion)	C7, C8	Flexor pollicis and digitorum profundus I, II	Median
Tip of ring and Vth finger flexion	C8	Flexor digitorum profundus IV, V	Ulnar
Thumb abduction	T1	Abductor pollicis brevis	Median
Finger abduction	T1	Dorsal interossei	Ulnar
Finger flexion	(C7), C8, (T1)	Long and short flexors	Median and ulnar
Hip flexion	L1, L2, (L3)	Iliopsoas	Nerve to iliopsoas
Hip adduction	L2, L3, L4	Adductor magnus	Obturator
Knee extension	L3, L4	Quadriceps femoris	Femoral
Ankle dorsiflexion	L4, L5	Tibialis anterior	Deep peroneal
Big toe extension	L5, (S1)	Extensor hallucis longus	Deep peroneal
Ankle eversion	L5, S1	Peroneal muscles	Superficial peroneal
Ankle inversion	L4, L5	Tibialis posterior	Tibial
Ankle plantar flexion	S1, S2	Gastrocnemius, soleus	Posterior tibial
Knee flexion	S1, (S2)	Hamstrings	Sciatic
Hip extension	S1, (S2)	Gluteus maximus	Inferior gluteal

affects all sacral roots streaming caudally. This causes loss of bladder and bowel control, numbness of buttocks and thighs with paralysis of ankle dorsiflexion (L4), toes (L4, L5), eversion and plantar flexion (S1). The S1 reflexes are lost (ankle jerks). This can occur rapidly over the course of several hours or less, sometimes with little back pain. An acute cauda equina syndrome is a potential neurosurgical emergency.

Difficulties can occur in the distinction between a cauda equina lesion and a lesion of the conus medullaris – the lowermost part of the cord, e.g. an MS plaque in the conus. In both, weakness, sensory loss and loss of sphincter control occurs. In an acute conus lesion lower limb reflexes are lost, as they are in a high cauda equina lesion. The emergence of extensor plantar responses and patterns of sensory loss typical of a cord lesion (sensory level in the abdomen, Brown-Séquard signs) usually enable distinction on clinical grounds.

Myopathy and neuromuscular junction disease

Muscle disease tends to produce symmetrical abnormalities. Details and difficulties in the diagnosis of muscle diseases are discussed in Chapter 9.

Inflammatory muscle disease (e.g. polymyositis) causes induration, pain and weakness. Dystrophies and most metabolic muscle diseases present typically with weakness alone; pseudohypertrophy (excessively bulky muscles) may be seen. Slow relaxation is a feature of myotonic conditions. Fatiguability is the characteristic of myasthenia gravis, and the reverse – increasing power on exercise sometimes a feature of LEMS.

Subacute paralytic conditions

This loose term is used to describe increasing weakness over the course of days, up to a wholly arbitrary period of 3 weeks. Spinal cord compression, poliomyelitis, Guillain–Barré syndrome, vasculitic neuropathies, myasthenia gravis, LEMS, botulism, periodic paralyses and MS are potential causes that require vigilance and specialist investigation (Chapters 8, 9 and 10).

Respiratory impairment is of critical importance and easy to miss in the face of severe progressive limb weakness. Such cases are some of the most challenging in acute neurology. Remarkably, even with widespread knowledge and understanding of these conditions, evidence indicates that initial paralytic symptoms are regarded as non-organic in about one-quarter of patients when they first seek help from a doctor.

Unexplained symptoms, abnormal illness behaviour and somatoform disorder

Symptoms that are unexplained or only partially explained by organic disease are features in 20–30% of new cases seen in any general neurology clinic. Many neurologists, especially in the distant past, have been tempted to think that deliberate symptom exaggeration and even fabrication are more frequent than they are thought to be today. The issue is that it is evident that many patients have symptoms that are worrying, painful, unpleasant or uncomfortable, but which do not reflect any serious underlying disease. This section briefly outlines one approach to symptoms of this nature. For example, unexplained fatigue, give-way weakness or paralysis and non-organic sensory loss are part of a spectrum of symptoms for which no organic disease is found. In a more psychiatric context, abnormal illness behaviour is a diagnosis in common use; the phrase not only implies that the patient complains about symptoms in a way believed to be disproportionate but also reflects the attitude and reactions of medical staff – for example, unnecessary admissions to hospital, investigations or treatment. For example, about half of cases of apparent status epilepticus seen in A&E and some 15% of cases of recurrent seizures referred to epilepsy specialist clinics are believed to be non-organic, but these conditions are treated initially, very largely as if they were seizures. These matters are also discussed in greater depth in Chapter 21.

The first suggestion is to accept and understand that the great majority of patients do have the symptoms of which they complain. This comment excludes those involved in legal claims, where non-organic features are especially prominent and of more doubtful nature. The second is to exclude organic disease with all reasonable certainty. Specialized tests may be necessary to do this. The third requirement, for all neurologists, is to understand the psychiatric diagnoses that might lead to or explain such symptoms. These include:

- Anxiety and depression.
- Somatization disorder – symptoms in more than one system, usually lifelong, such as irritable bowel, chronic fatigue or unexplained pain with the implication that psychological problems have been somatized.
- Hypochondriasis – a state of fear, distress and anxiety about possible disease.
- Conversion and dissociative disorder – motor or sensory symptoms thought to relate to psychological factors.
- Somatic manifestations of depressive illness or anxiety.

Factitious disorder (symptoms to gain medical attention) and malingering (symptoms for material gain) are also possible, if rare explanations.

However, in many cases of apparent illness behaviour, no formal psychiatric diagnosis is apparent.

The approach to anxiety and/or aggressive behaviour needs qualification. Anxiety is ubiquitous – we all experience it. Most symptoms do not reflect serious disease but fear of illness is widely spread. This may all seem obvious, but there remains a tendency to equate anxiety with non-serious problems. The reality is that substantial anxiety occurs as frequently in sinister as in less serious medical conditions. Basic understanding of symptoms of a non-organic nature is necessary before embarking on the more specialist areas of organic neurology described in subsequent chapters.

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4

Stroke and Cerebrovascular Diseases

Nicholas Losseff, Martin Brown, Joan Grieve

Introduction

Epidemiology

Stroke is a major public health problem, being the third most common cause of death after myocardial infarction and cancer, and the leading cause of adult disability. Stroke accounts for 11% of deaths in England and Wales. Every year about 110,000 people will have their first stroke and about 40,000 patients will have a recurrent stroke. About 24% of patients die within 30 days of their stroke. Stroke is more common than most people realize. Approximately one-quarter of 45-year-old men will have a stroke before they reach the age of 85 (Table 4.1). Stroke is a very labour-intensive and expensive condition to manage, mainly because of the long length of stay in hospital. At any one time, 1 in 5 acute hospital beds and one-quarter of long-term beds are occupied by stroke patients in the UK. The average length of stay in an acute hospital bed after stroke is about 28 days. Around half of all stroke survivors are left dependent on others for everyday activities: if a patient can return home, the burden on carers is significant.

About 5% of the UK National Health Service budget is spent on looking after stroke patients in England and Wales. The cost of looking after an individual patient with stroke is around £15,000 over 5 years. When informal care costs are included, this increases to around £30,000. Stroke will become increasingly expensive in the future because the number of people living with stroke will increase as the population of elderly people in many parts of the world continues to rise.

Stroke is also an important condition in young people and can occur at any age, including *in utero* and in the neonatal period (it is a major cause of cerebral palsy), in childhood and young adult life. One-quarter of all strokes occur in people below the age of 65.

The incidence and types of stroke vary in different racial groups. Asian people appear to have a higher incidence of intracranial atherosclerosis than Caucasians and the incidence rates of first ever stroke are higher in black people of African or Caribbean descent than Caucasian populations living in the same cities. However, whether these differences reflect genetic or social and environmental factors is uncertain.

Clinical approach to stroke

Stroke can be briefly defined as an acute focal neurological deficit resulting from vascular disease. The World Health Organization provides a longer definition: 'Rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer, or leading to death, with no apparent cause other than of vascular origin.' The use of the term stroke should be restricted to a description of the clinical event experienced by the patient. Appearances on brain imaging should not be described as showing a stroke, but instead the scan may show infarction or haemorrhage, which may either have been responsible for a stroke or may have been asymptomatic. Also, to say someone has had a stroke is not sufficient as a medical diagnosis. Accurate diagnosis of stroke requires the cerebral circulatory disturbance to be defined in terms of pathology (ischaemia, infarction or haemorrhage), its anatomical location within the brain (e.g. left middle cerebral artery territory) and the underlying mechanism (e.g. cardio-embolism). The task of the stroke physician is to make an accurate pathophysiological diagnosis in these terms to guide appropriate management. This requires a basic knowledge of the clinical and radiological patterns that different stroke syndromes produce and the underlying pathophysiology of stroke.

Stroke has traditionally been distinguished from transient ischaemic attack (TIA), the latter referring to focal neurological symptoms attributed to cerebral ischaemia lasting less than 24 hours, with complete recovery. The distinction is arbitrary. Some patients with TIA develop appropriately sited infarction on imaging despite rapid recovery of their symptoms, while others recover rapidly having had ischaemia evident on cerebral blood

Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

Table 4.1 Cumulative probability (%) of a 45-year-old person having a stroke before the age listed in the left-hand column.

Age	Men	Women
65	3	3
75	10	6
85	24	18
90	33	28

Table 4.2 Underlying pathology of stroke.

Pathology	Anatomical subdivision
Infarction	Small vessel (lacunar) infarction Total or partial territorial infarction Border-zone infarction
Intracranial haemorrhage	Lobar Deep/basal ganglia Posterior fossa
Subarachnoid haemorrhage	Aneurysm, AVM
Cerebral venous thrombosis	Vein, venous sinus

AVM, arteriovenous malformation.

flow studies. Many TIA cases both recover completely and have normal imaging and normal blood flow studies by the time of investigation. Most patients with TIAs recover within less than an hour. By definition, a stroke requires symptoms to have been present for over 24 hours, giving the impression that there is no hurry to make the diagnosis. In fact, those patients with acute neurological disturbances that may be the result of stroke require immediate assessment in hospital for consideration of reperfusion therapy, e.g. thrombolysis. Equally, patients with a recent history of TIA require urgent investigation and treatment to prevent a recurrence. The fact that a patient with a TIA appears to recover fully gives a false sense of security and that there is no urgency for assessment. However, in a UK population-based study in Oxfordshire, the average risks of recurrent stroke at 7 days, 1 month and 3 months after TIA were 8%, 12% and 17%, respectively. In patients with specific risk factors for recurrence, the 7-day risk may be as high as 31%. The need to emphasize these aspects of acute stroke and TIA has led to the use of the term 'brain attack' to emphasize to the public the urgency of the situation. It also has the value of emphasizing that acute focal neurological events have a differential diagnosis, in that stroke mimics will need to be distinguishable from stroke and TIA. The older term, cerebrovascular accident (CVA) should be avoided completely. Stroke is not accidental; the term CVA implies a negative approach to the patient and their illness.

The underlying pathology responsible for the persistent symptoms of stroke is either infarction or haemorrhage. Haemorrhage is subdivided according to location into intracranial haemorrhage and subarachnoid haemorrhage (Table 4.2). In about 85% of cases, stroke is secondary to infarction. When infarction involves only a small volume of the tissue (<1.5 cm in diameter on computerized tomography [CT]) secondary to occlusion of a penetrating artery, the resulting death of tissue is known as a lacune or a lacunar infarct. The underlying pathology responsible for lacunar infarction is often referred to as small vessel disease. This may also lead to asymptomatic changes on imaging of the deep white matter known as leuco-araiosis, discussed in more detail below. Lacunes are generally found in subcortical white matter or the basal ganglia. Larger infarcts usually involve a wedge of both cortical and subcortical white matter and result from occlusion of the trunk or branches of the major cerebral arteries, most commonly the middle cerebral artery (MCA). The size of infarction resulting from arterial occlusion will depend on the adequacy of the collateral supply via the circle of Willis and pial collateral vessels. Infarction may therefore affect all or only part of the territory of the occluded artery. Occasionally, infarction occupies the border-zones between arterial supplies, particularly if the infarction follows an episode of generalized reduction in cerebral blood flow (e.g. after cardiac arrest) or results from internal carotid artery occlusion. It is then known as border-zone or watershed infarction.

About 10% of acute strokes are caused by intracranial haemorrhage, i.e. within the substance of the brain. When the bleeding occurs from deep penetrating arteries, often secondary to small vessel disease, the centre of the haemorrhage is usually located within the basal ganglia, particularly the lentiform nucleus or the deep white matter tracts. More superficial haemorrhages are known as lobar haemorrhages and are more commonly caused by vascular malformations or cerebral amyloid angiopathy. In about 5% of cases, intracranial bleeding occurs primarily within the subarachnoid space. Subarachnoid haemorrhage is distinctive in that there may be no focal damage to the brain if the patient only has meningeal irritation, e.g. headache and/or neck stiffness. Subarachnoid haemorrhage is therefore not always classified as a form of stroke. However, the arguments are stronger in favour of including subarachnoid haemorrhage within the definition of stroke, because subarachnoid haemorrhage may be accompanied by intracranial haemorrhage with focal deficits. Also, subarachnoid bleeding frequently causes constriction of the intracerebral arteries, known as vasospasm, which can result in cerebral infarction with focal symptoms identical to that seen in other causes of ischaemic stroke.

The well-known vascular risk factors, e.g. hypertension, diabetes and smoking, are not in themselves causes of stroke, but instead promote the development of the underlying pathological processes, e.g. atherosclerosis, responsible for stroke. Their importance is therefore to provide targets for interventions to prevent stroke, rather than in diagnosis.

The majority of strokes result from arterial pathology but a small proportion, less than 1%, result from cerebral venous thrombosis. Although rare, this is an important cause to recognize because of the need for specific investigations and treatment. Cerebral venous thrombosis may cause isolated cerebral infarction, haemorrhagic infarction, intracerebral haemorrhage or subarachnoid haemorrhage. Venous thrombosis can also present with raised intracranial pressure and epileptic seizures without focal cerebral features.

It is usually impossible to distinguish reliably between infarction and intracranial haemorrhage from the history and examination, although the features of subarachnoid haemorrhage are usually distinct. Cranial imaging is the only reliable method to distinguish between infarction and haemorrhage. Imaging also plays a major part in confirming the anatomical location of the pathology. The location may also provide clues to likely mechanisms. Other investigations are required to establish the underlying mechanism of the infarction or haemorrhage in order to plan appropriate treatment and prevention.

Medical assessment of the stroke patient on admission should concentrate on establishing the diagnosis in terms of pathology, anatomy and mechanism. It is important that initial assessment and the response to treatment and therapy should include an assessment of the patient's functional abilities, as well as their neurological examination. Validated scoring systems have been developed specifically for use in stroke patients. The most widely used scores for neurological impairment, based on the standardized neurological examination, are the Scandinavian Stroke Scale and the National Institutes of Health Stroke Scale (NIHSS). The most widely used functional outcome scores are the Barthel Index and the Modified Rankin Scale. A number of schemes have also been developed to assist in classifying subtypes of stroke. These include the Oxfordshire Community Stroke Project Classification, which divides stroke on clinical features alone into total anterior cerebral infarction (TACI, usually total middle cerebral artery territory infarction), partial anterior territory infarcts (PACI), lacunar infarcts (LACI) and posterior cerebral infarction (POCI). However, this classification is not particularly accurate in the first few hours after onset and only predicts the size of infarction on imaging in about three-quarters of patients. A more specific approach, originally developed for use in a clinical trial, is known as the TOAST Classification. This divides ischaemic stroke on the basis of detailed investigations, into atherothrombotic, cardio-embolic, small vessel occlusion, other determined cause and undetermined cause.

Ischaemic stroke

Important vascular anatomy

Heart and great vessels

The left ventricle gives rise to the ascending aorta and then its arch. Arising from the arch from right to left are the innominate, the left common carotid and the left subclavian arteries. The innominate bifurcates into the right subclavian, which gives off the vertebral and the right common carotid artery. The left subclavian gives rise to the left vertebral (Figure 4.1).

It therefore makes sense that embolic material arising from the heart or ascending aorta can enter any vessel or combination of vessels. An innominate plaque of atherosclerosis may cause embolism within the right carotid and right vertebral territory.

Extracranial and intracranial arteries

The internal carotid arteries (ICAs) begin in the neck at the carotid bifurcation, usually near the angle of the jaw, and ascend cranially. Note that it is the common carotid pulse that is palpated in the neck. The ICAs travel behind the pharynx but give off no branches in the neck. This makes them readily identifiable on angiography and distinct from the external carotid arteries which do branch. The ICAs enter the skull through the carotid canal in the petrous bone and then pass through the cavernous sinus. The cavernous carotid gives off the ophthalmic artery and then pierces the dura. The supraclinoid portion of the carotid gives off the anterior choroidal and posterior communicating artery before

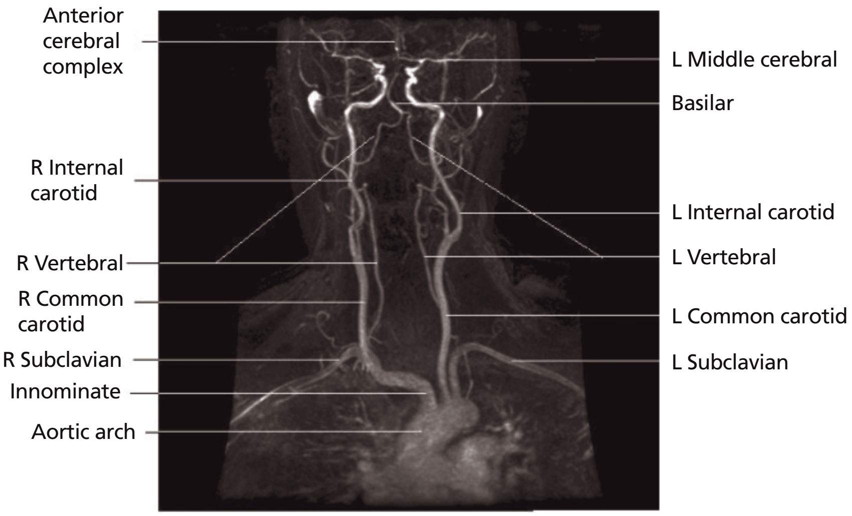

Figure 4.1 Great vessels, cervical and major intracranial arteries (contrast-enhanced magnetic resonance angiogram [MRA]).

bifurcation into anterior and middle cerebral arteries. The external carotids give branches to the neck, face and scalp. Some of these are easily palpated, e.g. the superficial temporal artery. The external carotids can act as a collateral blood supply to the hemisphere via meningeal branches, especially in the event of ICA occlusion. Often, the only clinical symptom of this is a throbbing unilateral temporal headache caused by diversion through superficial channels. Biopsy this at your peril.

The anterior choroidal arteries are small and course posteriorly along the optic tract. They give off branches to a zone between the other internal carotid branches (anterior and middle cerebral artery) and vertebral circulation. They supply perforating branches to the globus pallidus, posterior limb of the internal capsule, temporal lobe, thalamus and lateral geniculate body.

The anterior cerebral arteries (ACAs) course medially then run posterior over the corpus callosum. They supply the anterior and medial portions of the hemispheres, basal frontal lobes and caudate. Within the cortical territory of the ACA is the leg area of the homunculus. The two ACAs are usually joined together by an anterior communicating artery (ACOM) and there are various anatomic variations that dictate the pattern of ischaemic damage. In carotid occlusion the ACA territory is often spared because of collateral supply from the ACOM. If there is no ACOM then this mechanisms fails. Sometimes, both anterior cerebral arteries are supplied by a single carotid, so carotid occlusion may infarct both ACA territories or neither.

The MCAs course laterally after their origin; the proximal MCA trunk gives off numerous penetrating lenticulo-striate arteries to the basal ganglia and internal capsule. Near the Sylvian fissure the MCA trifurcates into small anterior temporal branches and large superior and inferior trunks. The superior trunk supplies the lateral portion of the hemisphere above and the inferior trunk the portion below the Sylvian fissure. Amongst its cortical supply the MCA supplies the arm area of the homunculus.

The vertebral arteries arise from each subclavian and are unusual in that they anastomose to form a larger artery, the basilar (Figure 4.2). The vertebral arteries course upwards and backwards entering the transverse foramina at C5 or C6. They run up through the intravertebral foramina exiting to pierce the dura and enter the foramen magnum. Their intracranial portions anastomose at the ponto-medullary junction to form the basilar artery. In the neck the vertebral arteries give off many spinal and muscular branches. The intracranial vertebral gives rise to the posterior and anterior spinal arteries, penetrating branches to the medulla and the posterior inferior cerebellar arteries. The basilar then runs up in the midline giving off the bilateral anterior inferior, superior cerebellar arteries and penetrating branches to the brainstem. At the ponto-mesencephalic junction the basilar terminates into posterior cerebral arteries. The posterior cerebral arteries give off perforating branches to the midbrain and thalamus, course around the cerebral peduncles and then supply occipital and inferior temporal lobes. The anatomy of the vertebral circulation is more varied than that of the carotid. Commonly, one vertebral is hypoplastic or may terminate in the posterior inferior cerebellar artery (PICA).

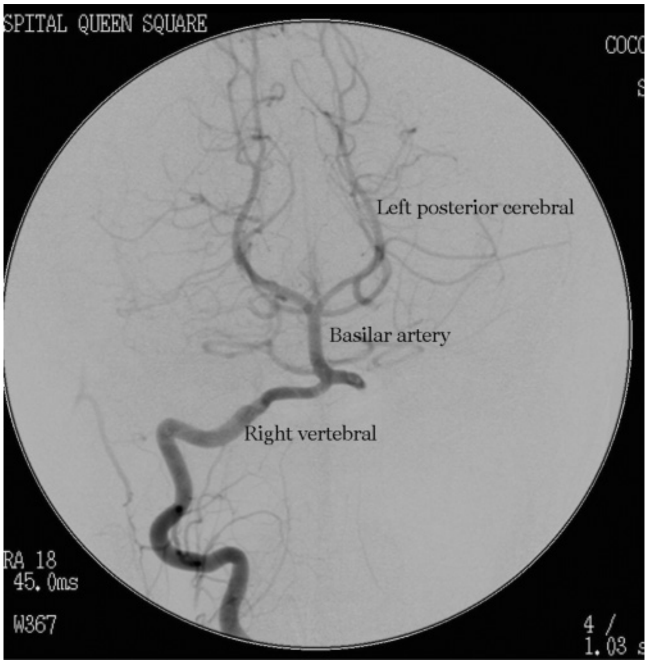

Figure 4.2 Vertebro-basilar circulation (catheter angiogram).

The anterior, middle and posterior cerebral arteries are connected via communicating vessels and all these vessels together form the circle of Willis.

Venous anatomy

The cerebral veins may be divided into the venous dural sinuses and the superficial and deep venous systems. The dural sinus walls are formed by the layers of the dura itself and are situated at the junction of the falx and tentorium. The intracranial veins drain into the sinuses which then drain into the jugular veins. The ophthalmic and facial veins drain into the cavernous sinuses which lie symmetrically in the parasellar region. The important venous sinuses are the midline sagittal and straight sinus and the transverse sinuses (Figure 4.3).

Pathophysiology of ischaemic stroke

Thrombosis, embolism and hypoperfusion

There are three potential mechanisms of ischaemic stroke: thrombosis, embolism and hypoperfusion (haemodynamic failure). While these are inter-related, each mechanism can produce distinct clinical syndromes. It is important to think about these mechanisms when assessing patients as ultimately this guides treatment.

The effect of a localized blood vessel occlusion will depend on the following factors: the area of brain supplied by the vessel, the nature of the occlusion, the time that the occlusion lasts, its degree and anatomy of collateral circulation. Consider how these factors interact: one patient has a 95% internal carotid stenosis on which

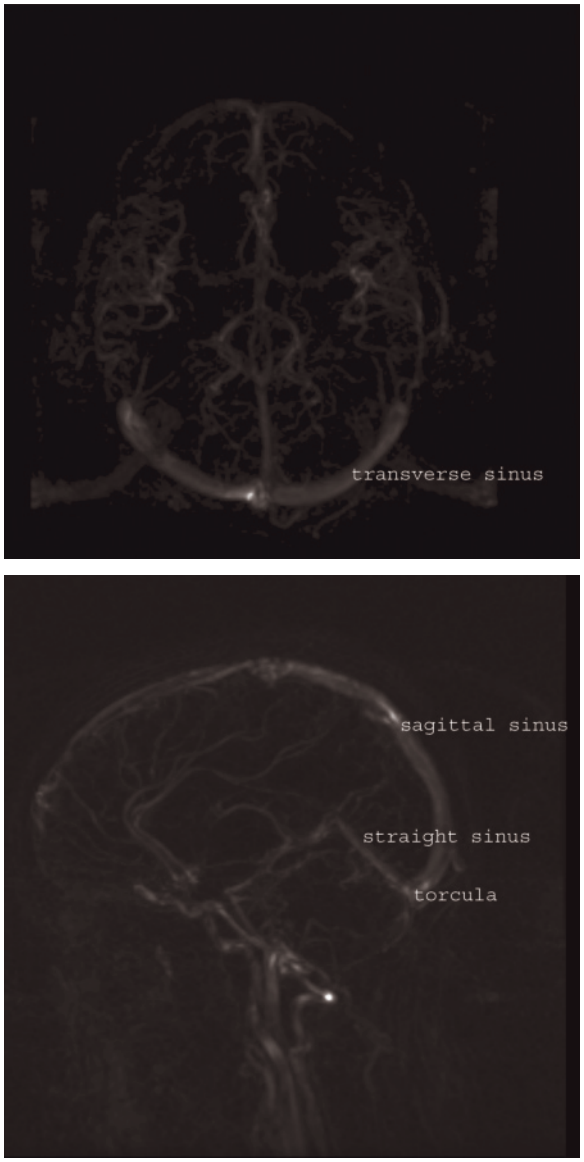

Figure 4.3 Venous anatomy (MRA).

a thrombus forms occluding the vessel. There may be no effects if this thrombosis remains localized (i.e. does not embolize to the brain) and the collateral circulation to the hemisphere above the occluded carotid is adequate. Conversely, even if the thrombosis remains localized, the absence of an effective collateral circulation may result in infarction of the whole of the carotid territory. If the collateral circulation is poor, then the most vulnerable areas will infarct; these are the areas with the poorest perfusion pressure and furthest away from the occluded artery. An example is shown in Figure 4.4 as a linear area of infarction in the border-zone between the anterior and middle cerebral artery territory. The occluded carotid is very unlikely to recanalize as the obstruction is principally hardened atheroma.

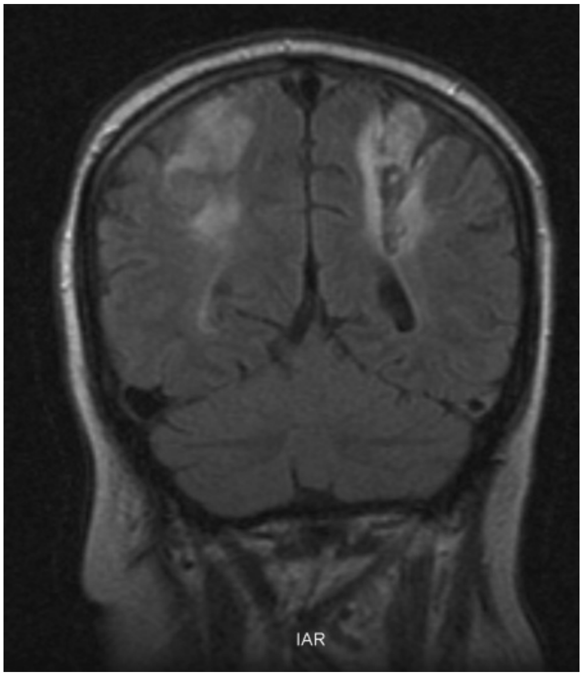

Figure 4.4 Border-zone infarction following carotid occlusion (Coronal MR FLAIR image).

Another scenario is this: on the roughened surface of the 95% stenosis, platelets activate to form a white thrombus which embolizes to the brain. The thrombus may lodge in the origin of the anterior cerebral artery and have no effect because the territory has an adequate collateral circulation via the anterior communicator. Maybe it lodges at the origin of the MCA for an hour before it lyses. The meningeal collaterals over the surface of the hemisphere maintain some cortical areas for the time but the lenticulostriate perforators arising from the MCA origin are all blocked and the deep territory fails rapidly as there is no collateral blood supply. The deep territory has irreversibly infarcted but the superficial collateralized territory is hanging on. Unfortunately, the patient develops a pneumonia and becomes hypotensive: the tenuous collaterals can no longer perfuse the hemisphere. The entire hemisphere infarcts.

Stenosis and occlusion are distinct. Occlusion of a vessel may occur without pre-existent stenosis or other localized disease. This is usually a result of embolism from the heart, while arterial stenosis (e.g. of the internal carotid) is a risk factor for occlusion upstream by atheroembolism (e.g. MCA occlusion).

Thrombosis is difficult distinguish from embolism, but hypoperfusion may be more easily recognizable. However, it is important to think about the macroscopic mechanisms of ischaemia. It is unlikely that an occluded atheromatous carotid will recanalize with thrombolysis, but if the patient has border-zone ischaemia, then keeping up their blood pressure may help. Conversely, thrombolysis of fresh red cardio-embolic thrombus obstructing the proximal MCA is a practical proposition.

Patterns of stroke are discussed in detail later. The adequacy of collateral circulation depends not only on systemic perfusion pressures, but many factors including one's anatomical make-up and small as well as large blood vessels diffusely damaged by diabetes or hypertension.

Microscopic and metabolic changes

The brain is metabolically a highly active organ. Although it accounts for only 2% of body weight, it uses 20% of cardiac output when the body is at rest. Brain energy use is also dependent on the degree of neuronal activation. The brain uses glucose exclusively as a substrate for energy metabolism by oxidizing this to carbon dioxide and water. This metabolism allows conversion of adenosine diphosphate to adenosine triphosphate (ATP). A constant supply of ATP is essential for neuronal integrity and this process is much more efficient in the presence of oxygen. Although ATP can be formed by anaerobic glycolysis, the energy yielded by this pathway is small and it also leads to the accumulation of lactic acid. The brain needs and uses approximately 500 mL oxygen and 100 mg glucose each minute, hence the need for a rich supply of oxygenated blood containing glucose. Cerebral blood flow (CBF) is normally approximately 50 mL/minute for each 100 g of brain. By increasing oxygen extraction from the blood adequate compensation can be made even if blood flow is reduced to approximately 20–25 mL per 100 g/minute. Sophisticated systems exist that allow the cerebral circulation to maintain constant levels of CBF in the face of changing systemic blood pressure, usually called autoregulation. In the healthy state, CBF remains relatively constant when mean arterial blood pressure is 50–150 mmHg.

As cerebral blood flow falls, metabolic paralysis ensues and this may be reversible. However, if prolonged, infarction is inevitable. When CBF falls below 20 mL/100 g/minute, oxygen extraction starts to fall and changes may be detected on electroencephalography (EEG). At levels below 10 mL/100 g/minute, cell membrane functions are severely disrupted. Below 5 mL/100 g/minute, cell death is inevitable within a short time.

When neurones become ischaemic, a cascade of biochemical changes potentiate cell death. These pathophysiological changes have been of considerable interest to those developing treatments to lessen the damage caused by ischaemic stroke. In the ischaemic brain, ion channels fail, K^+ moves out of the cell into the extracellular space and Ca^{2+} moves in, where it further compromises the ability of the cell to maintain ionic homeostasis and leads to mitochondrial failure. Hypoxia leads to the generation of free radicals which peroxidize fatty acids in cell membranes causing further cell dysfunction. Anaerobic glycolysis results in lactic acidosis further impairing cellular metabolic functions. Excitatory neurotransmitter activity (e.g. glutamate) is greatly increased in areas of brain ischaemia because of increased release and failure of uptake mechanisms. These neurotransmitters are themselves toxic at these increased levels by causing further Ca^{2+} and Na^+ influx into cells through their actions on NMDA receptors. Hence, ischaemia triggers a vicious cascade of events leading to cell electrical failure and then death. At some point the process becomes irreversible even after reperfusion of tissues. Even if the severity of ischaemia is inadequate to cause necrosis, it may trigger apoptosis.

Ischaemic penumbra

The degree of ischaemia caused by blockage of an artery varies, partly depending on collateral supply. At the centre of an infarct the damage is most severe but at the periphery collateral flow may allow continued delivery of blood, although at a lower rate. This zone may become dysfunctional secondary to electrical failure although not dead and is referred to as the ischaemic penumbra. In any solar or lunar eclipse there is an umbra (the dense shadow) and the penumbra surrounding it. It is this outer zone that is further at risk following the onset of stroke. Sophisticated imaging can now define areas of irreversible brain damage and areas in which perfusion is suboptimal but where irreversible infarction has not taken place. The penumbra is the area of brain with the potential to survive. It is entirely likely that high-quality simple supportive management in the acute stage decreases the degree of this further secondary brain damage.

Pressure changes

Energy failure results in cytotoxic oedema where water accumulates inside cells. This is the radiological hallmark of early cerebral infarction and its distribution obeys vascular territories, unlike vasogenic oedema (extracellular accumulation) which spreads along white matter tracts. Significant brain swelling follows cytotoxic oedema increasing intracranial pressure and further decreasing CBF (Figure 4.5). Ultimately, coning may occur, after massive brain infarction or there may be important local pressure effects (e.g. brainstem compression following cerebellar infarction).

Risk factors and causes of ischaemic stroke

Ischaemic stroke is the result of vessel occlusion from *in situ* thrombosis, embolism or haemodynamic failure. Embolism may be from artery to artery (30–40%) or from the heart (30–40%). In 25% disease of the walls of small penetrating intracranial blood vessels is responsible for lacunar infarction.

Hence, the main risk factors for stroke are the risk factors for atheroma and heart disease (Table 4.3). Non-atherosclerotic vasculopathies and primary haematological disease are much less common.

Both the clinical syndromes and risk factors of lacunar stroke and large vessel occlusion overlap. Stroke is usually the result of a combination of risk factors coming together rather than a single entity.

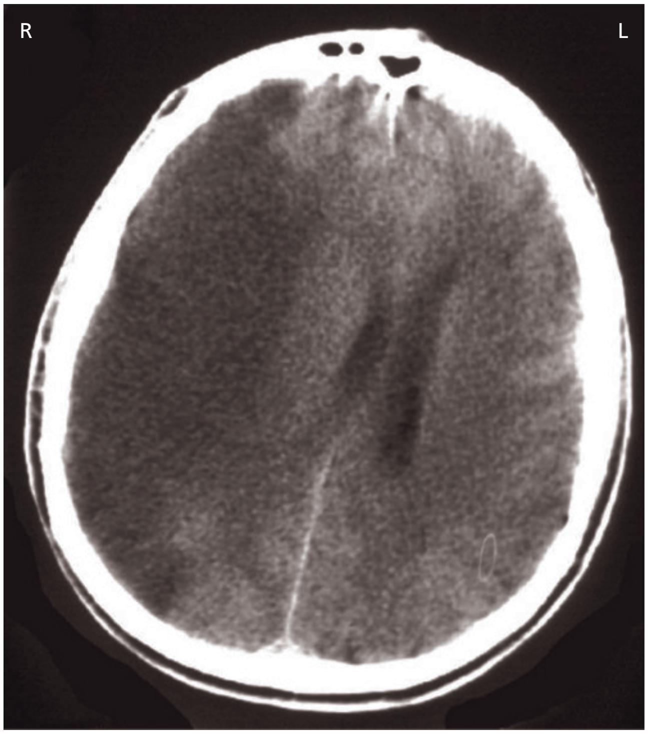

Figure 4.5 Cytotoxic oedema with brain swelling following right MCA occlusion (unenhanced CT).

Table 4.3 Major risk factors.

Age
Hypertension
Smoking
Diabetes mellitus
Atrial fibrillation
Heart disease
Dyslipidaemia
Alcohol
Obesity
Symptomatic and asymptomatic carotid stenosis
Drug misuse

Age, hypertension, smoking, lipids and drug misuse

The incidence of stroke rises dramatically with age, doubling each decade past 55 years. Half of all stroke occurs in the over-70 age group. At least 25% of the adult population have hypertension >140/90 mmHg. After age, this is the most important and modifiable risk factor. The Framingham data show a linear relationship between risk of stroke and arterial hypertension and this effect is seen across all levels of blood pressure.

Smoking remains a leading preventable cause of death and an independent risk factor for stroke. It particularly predisposes to carotid stenosis in men. Diabetes mellitus increases the risk of stroke by about two- to fourfold when compared with those without diabetes. The excess diabetic risk is independent of age and blood pressure status. High total cholesterol and low-density lipoprotein (LDL) correlate with atherosclerosis. Although low levels of high-density lipoprotein (HDL) correlate well with coronary artery disease, the relationship is less clear for cerebrovascular disease. Alcohol consumption demonstrates a J-shaped relationship; heavy drinking being associated with a higher risk of all stroke, both ischaemic and haemorrhagic. The presence of asymptomatic carotid disease carries a greater cardiovascular than cerebrovascular risk. Asymptomatic stenosis of greater than 75% carries an annual stroke risk of only 2% or less. In contrast, if the stenosis is recently symptomatic, the annual risk increases to 15% and is even higher if the stenosis is greater or the symptoms very recent. This is discussed in greater detail in the section on secondary prevention. Plaque structure rather than the degree of narrowing is important, with ulcerated heterogeneous plaques being more likely to rupture or allow thrombosis on their surface. Drug-related stroke is an increasing problem and may be multi-factorial. The mechanisms of stroke after drug misuse are very broad (Table 4.4).

Table 4.4 Mechanisms of stroke associated with drug misuse.

Complications of parenteral administration, e.g. heroin, cocaine
Infective or non-bacterial (marantic) endocarditis – infarction or haemorrhage from associated mycotic aneurysm
Direct embolization of particulate matter – infarction via right to left shunt (e.g. patent foramen ovale or pulmonary shunt) or from direct carotid administration
Acute severe hypertension (TIA, infarction or haemorrhage)
Arterial vasospasm (infarction or TIA), e.g. crack cocaine, cocaine, amphetamine, possibly cannabis
Arterial dissection
Hypersensitivity vasculitis: associated with amphetamine, heroin, cocaine and crack cocaine (headache encephalopathy, stroke-like episodes, seizures) – all rarely proven

TIA, transient ischaemic attack.

Another effect of drugs of abuse is rupture of a coincidental underlying aneurysm or arteriovenous malformation. This is a common cause of intracranial cerebral haemorrhage (ICH; either subarachnoid or parenchymal) in users of stimulant drugs (e.g. amphetamine, crack and cocaine). All patients with drug-related subarachnoid haemorrhage (SAH) or ICH need careful evaluation to exclude such causes based on the pattern of haemorrhage. In some patients, induction of antiphospholipid antibodies has been associated with cocaine and heroin. Whether they confer a specific risk is not clear and it must be noted that antiphospholipid antibodies are also associated with infection and vasculopathies of many causes.

Cardiac disease

Heart disease may be divided into high or low risk. Atrial fibrillation remains the most important cause of cardio-embolism (Table 4.5).

Table 4.5 Cardiac causes of stroke.

High risk	Atrial fibrillation (especially combined with other risk factors) Valvular heart disease Prosthetic heart valves Bacterial endocarditis Non-infective (marantic) endocarditis (Chapter 20) Cardiac surgery
Low risk	Myocardial infarction Ventricular/atrial aneurysm Cardiomyopathy (e.g. amyloid, alcohol, cocaine) Septal abnormalities (e.g. ASD, patent foramen ovale, atrial septal aneurysm)
Rare	Intracardiac lesions (myxoma, fibroelastoma)

ASD, atrial septal defect.

Atrial fibrillation is a common cardiac disorder, with up to 5% of the over-60-year-olds affected. Atrial fibrillation is an important risk factor for stroke, with a general risk of about 4% per year in patients who have not had prior embolic symptoms and about 12% per year in patients with prior TIA or stroke. Other coexistent risk factors (e.g. age, hypertension or left ventricular dysfunction) also increase the risk. Sick sinus syndrome through atrial dysfunction may also result in embolism. As many as 10–20% of patients with valvular hear disease have a stroke as the abnormal valve surface promotes thrombosis and embolization. The most important used to be rheumatic mitral stenosis but this is now overtaken by endocarditis on native or prosthetic valves. The manifestations of endocarditis are protean and include ischaemia, ICH and SAH, encephalopathy and meningitis. Endocarditis is much more common on prosthetic valves and often resistant to treatment. Non-infective endocarditis was first described by Libman and Sacks; the condition spans simple valve thickening to frank vegetations containing platelets and fibrin. Systemic lupus erythematosus (SLE), antiphospholipid syndrome and malignancy are potential causes.

After myocardial infarction (MI), there is a systemic embolism rate of about 3%. Most emboli will affect the brain. Most thrombi arise in the ventricle after anterior MI. Left ventricular thrombi can be detected in approximately 30% of patients after anterior MI. The thrombi develop within 3 days and embolism occurs on average 2 weeks after MI. Stroke is therefore rarely the presenting feature of MI, but this can occur in patients who have had an asymptomatic (silent) MI. The risk of stroke associated with impaired cardiac function is substantial.

Paradoxical embolus resulting from venous thrombosis entering the arterial circulation is an increasingly recognized and potentially important cause of stroke. However, in patients with a potential route for paradoxical embolism and stroke (e.g. patent foramen ovale), it is often not clear if emboli have been formed *de novo* in the heart or arose in the venous circulation, e.g. from deep vein thrombosis, to cause paradoxical embolism, or whether the stroke is unrelated to the cardiac abnormality. However, a classic triad is recognized that suggests true paradoxical embolism:

1 There is a reason for a venous thrombus (e g. taking the oral contraceptive pill);

2 The stroke happens at a time when shunting and paradoxical embolus are possible (e.g. during a Valsalva); and

3 The stroke syndrome is typically cardio-embolic (e.g. posterior cerebral artery occlusion or small cortical infarct).

The most common potential intracardiac shunt is patent foramen ovale (PFO). However, this is present in about 25% of the population, making its presence difficult to put into context. In young apparently idiopathic stroke, the incidence of PFO approaches 50%. Recent studies suggest PFO alone after stroke carries a small 2% risk per year of further stroke. However, this seems to be increased to 15% by the concomitance of an atrial septal aneurysm, suggesting that this may be the main source of embolism.

Table 4.6 Haematological causes of stroke.

Important	Sickle cell disease Polycythaemia of any cause Thrombocythaemia Antiphospholipid antibody syndrome
Rare	Thrombotic thrombocytopenic purpura Paroxysmal nocturnal haemoglobinuria Leukaemia and myeloma
Uncertain (except by cerebral venous thrombosis or paradoxical embolus)	Activated protein C resistance +/– factor V Leiden mutation Protein C Protein S Antithrombin III deficiencies Prothrombin G20210 mutation Other thrombophilias
Other causes of hypercoagulability	Malignancy (especially stomach cancer) Vasculitis Homocystinuria Drugs (e.g. contraceptive pill, intravenous immunoglobulin) Nephrotic syndrome Disseminated intravascular coagulation

Stroke and the blood

Many haematological conditions can lead to stroke (Table 4.6), especially when other risk factors are present.

Sickle cell disease may produce stroke in childhood by intracranial stenosis and occlusion of the terminal carotid and proximal MCA. A channel of friable collaterals may form at the skull base (secondary Moyamoya syndrome, see below). In adults with sickle cell disease, ischaemic stroke is more frequently caused by small vessel disease or occlusion and often several other risk factors are present. There are many neurological phenomena associated with sickling and stroke is only one of them. Migrainous symptoms are common in patients with sickle cell disease.

Of the hypercoagulable states thrombophilia is commonly tested for in younger patients but rarely proven as a cause of stroke. Cerebral venous thrombosis is a far more likely mechanism of stroke associated with thrombophilia, but the latter may be relevant if there has been paradoxical arterial embolism. It is much more important to request a full blood count looking for polycythaemia and thrombocythaemia than a thrombophilia screen. The most common detectable abnormality in the population is activated protein C (APC) resistance; the others are very rare. Resistance to APC is one of the most commonly identified venous thromboembolic risk factors but there is no clear relationship to arterial stroke. APC resistance is inherited in a dominant fashion and in most patients associated with a single point mutation in the factor V gene (factor V Leiden). Patients may be homozygous or heterozygous.

Antiphospholipid antibodies and syndrome

One distinct haematological condition is the antiphospholipid antibody syndrome (APAS) in which arterial stroke is well documented. This is not the same as having antiphospholipid antibodies which may occur in association with other vasculopathies including atherosclerosis. Antiphospholipid antibodies have a pathogenic role in arterial and venous thrombosis. Ischaemic stroke is the most common arterial thrombotic event with APAS. Other neurological manifestations include neuropsychiatric features, movement disorders and migrainous headaches. There may be recurrent fetal loss and livedo reticularis. Antiphospholipid antibodies may be inferred by the presence of a circulating lupus anticoagulant or IgM and IgG antibodies. These antibodies may be present in patients with SLE, chronic infection and neoplasia but a rare subgroup has primary APAS with no other associated disease.

Non-atherosclerotic vasculopathies and other rare cases of stroke are discussed elsewhere in this chapter and in Chapter 25 (Table 4.7).

Table 4.7 Non-atherosclerotic vasculopathies.

Idiopathic/traumatic arterial dissection
Drug misuse
CADASIL
Mitochondrial disease
Arterial dissection secondary to identifiable collagen disease
Fibromuscular dysplasia
Vasculitis
Collagen vascular disease
Sneddon's syndrome
Susac's syndrome
Cervical/cranial irradiation
Moyamoya syndrome
Associated with acute or chronic meningitis and viral infection
Syphilis, malaria
HIV infection

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leuco-encephalopathy.

Clinical syndromes of cerebral ischaemia

Transient ischaemic attacks

We have tended to distinguish TIAs from completed stroke on an arbritary basis but the pathophysiology behind the cause may be identical (e.g. severe carotid stenosis) and both require urgent specialist assessment and investigation. The term brain attack, used by some to describe the acute presentation of TIA and stroke, emphasizes urgency. Careful history, examination and sophisticated neuroimaging often reveal that what has been labelled as a TIA is in fact associated with infarction. It is nevertheless useful to distinguish transient as opposed to persistent symptoms and signs, as the differential diagnosis of transient events is different.

The symptoms of transient ischemia are usually negative, maximal at onset and last typically for a few to 20 minutes.

The definition of TIA allows the symptoms to persist for up to 24 hours. We often think of transient ischaemia as indicating atherosclerosis within a specific arterial territory but TIAs may occur in the setting of multiple risk factors without imaging evidence of vasculopathy; or they may occur secondary to a haematological cause (e.g. antiphospholipid antibody syndrome). High-frequency attacks (several a week) are likely to be brought about by embolism from severe stenosis of a large artery; very high-frequency attacks (several a day) tend to follow from intermittent haemodynamic failure above a critically stenosed artery with poor flow. Such haemodynamic attacks may be distinguished by their diurnal variation (more common in the morning) and at times when blood flow is diverted elsewhere in the body, e.g. after eating or on exercise. Sometimes they present with limb jerking, similar to a focal motor seizure, that then gives way to weakness.

As a general rule, if a patient has more than three TIAs there should be an identifiable reason for them. If there is not a good reason evident after thorough investigation, then the diagnosis should be questioned. Common sites often ignored are found by examining the heart in detail (by trans-oesophageal echocardiography, TOE), the aortic arch (also best seen on TOE), the great vessels, the vertebral artery origins (difficult to image non-invasively) and the intracranial circulation.

TIAs are associated with a high rate of subsequent stroke: one-third of all untreated patients subsequently have a stroke. The immediate risk is high: 20% of strokes occur within a month and 50% within a year.

Within the carotid circulation (Table 4.8) the retinal circulation may be affected leading to transient monocular blindness (amaurosis fugax). This is usually described as a curtain or shutter coming down over one eye. Blindness usually lasts several minutes only; very occasionally, cholesterol emboli (a Hollenhorst plaque) may be seen after or during an attack. Hemisphere ischaemia is suggested by sudden onset contralateral weakness or dysphasia, when the dominant hemisphere is affected. The symptoms of hemisphere ischaemia usually last up to 20 minutes. Sensory loss in isolation is less common.

Within the vertebrobasilar circulation, attacks may cause diplopia, facial or tongue numbness, dysarthria, vertigo and bilateral visual loss. In some cases it is not possible to decide whether anterior or posterior circulation has been affected: an innominate stenosis with embolism (rare) may produce attacks with mixed features.

Table 4.8 Symptoms of transient ischemia and other symptoms not of transient ischaemia.

Symptoms of transient ischemia	
Carotid territory	Monocular visual loss
	Unilateral weakness
	Dysphasia
Vertebrobasilar	Diplopia
	Vertigo/dysequilibrium
	Bilateral visual loss
	Bilateral weakness
Either	Headache
	Dysarthria
	Hemianopia
	Unsteadiness
	Sensory loss
Symptoms not usually suggestive of transient ischaemia	
Syncope	
Isolated amnesia	
Drop attacks	
Generalized weakness	
Confusional states	
Isolated vertigo	

It is very unusual for isolated vertigo (Chapter 14) to be caused by vertebrobasilar ischaemia but not impossible – after all, infarction may be asymptomatic. Isolated vertigo is usually the result of an isolated vestibulopathy.

TIAs are unlikely to be caused by haemorrhage, although occasionally microhaemorrhages (small foci of susceptibility artefact visible using T2* gradient echo MRI but not on conventional MRI or CT) are associated with TIAs (Figure 4.6). These patients usually have uncontrolled hypertension.

Alternative diagnoses

About a quarter of people attending specialist cerebrovascular clinics with possible TIAs have alternative diagnoses. The most common is migraine with focal symptoms. These are either part of an aura preceding headache (not usually confused with TIAs), or without headache (commonly confused) or following a migrainous headache – the extremely rare hemiplegic migraine. Stroke itself and TIAs are not infrequently accompanied by headache. Some serious conditions may cause both migrainous symptoms and infarction, e.g. cervical artery dissection, APS and giant cell arteritis.

The two main pointers toward migraine are positive phenomena and spread. Visual aura may consist of zigzag lines and scintillating scotomas. Sensory aura is tingling rather than numbness and in a mouth–hand distribution. Patients may complain of weakness but this is usually vague. Symptoms evolve slowly – taking several minutes for the visual disturbance to maximize, or for the tingling to spread from the hand to the face (the typical distribution). True hemiplegic migraine (Chapter 11) is a rare familial channelopathy and quite distinct from other forms of migraine.

Other commonly confused conditions are transient global amnesia and epilepsy. Transient global amnesia (TGA) is sometimes precipitated by Valsalva activated straining, e.g. immersion

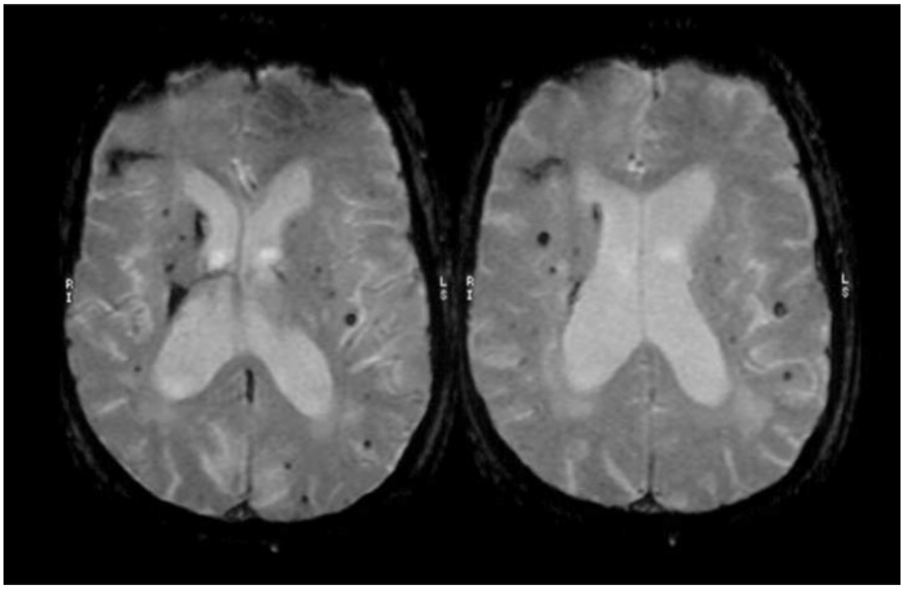

Figure 4.6 Multiple microhaemorrhages (MRI T2W).

Table 4.9 Differential diagnosis of transient ischaemia.

Migraine
Transient global amnesia
Epilepsy
Multiple sclerosis
Mass lesions, subdurals
Hypoglycaemia
Syncope

in cold water, travel or emotional stress. Hanging up curtains is one common precursor. Generally, in TGA, acute anterograde amnesia develops and patients usually appear bewildered and ask repetitive questions such as 'Where am I?' and 'What's going on?' There is no loss of personal identity as in a fugue state. The attacks last several hours and after recovery the patient has little recollection of the event. TGA is a heterogeneous disorder but in general is benign and not associated with a subsequent stroke risk. There does seem to be a subgroup of patients with small vessel disease underpinning the disorder and even rarer transient epileptic amnesia. Patients should be investigated with imaging and for vascular risk factors.

In addition, other serious intracranial pathology may cause transient symptoms such as tumours, subdural haematomas and multiple sclerosis. Hypoglycaemia may masquerade as all sorts of transient neurological disturbances but is rare in practice. Syncope can sometimes produce confusing clinical pictures including focal deficits.

Investigation when true transient ischemia is thought possible is the same as for completed stroke and is discussed below.

Lacunar stroke

Lacunes are small, subcortical or brainstem infarcts ranging 1–15 mm in size. They need to be distinguished from the dilated peri-vascular spaces commonly visible on MRI. This is easy with MR FLAIR imaging: although both may be white on T2, lacunes are also white on FLAIR, whereas a peri-vascular space is black. Lacunar infarction is caused by occlusion of small penetrating vessels most commonly arising from the MCA and basilar artery (Figure 4.7). Lacunes may be silent. They may be preceded by TIAs in some 20%; sometimes these are high-frequency attacks refractory to all treatments (capsular warning syndrome). Lacunar TIAs tend to be briefer and more stereotyped than large vessel TIAs. The two pathologies underlying vessel occlusion are usually lipohyaline change and/or microatheroma. Although lacunar infarction is also associated with carotid stenosis, it does not commonly happen as an embolic syndrome. The major risk factors for lacunar stroke are hypertension, diabetes and hypercholesterolaemia. Occlusion of small penetrating vessels is commonly asymptomatic but if eloquent structures are involved then the syndromes are fairly stereotypic. The most common sites for lacunar infarction are the putamen, pallidum, pons, thalamus, caudate, internal capsule and corona radiata.

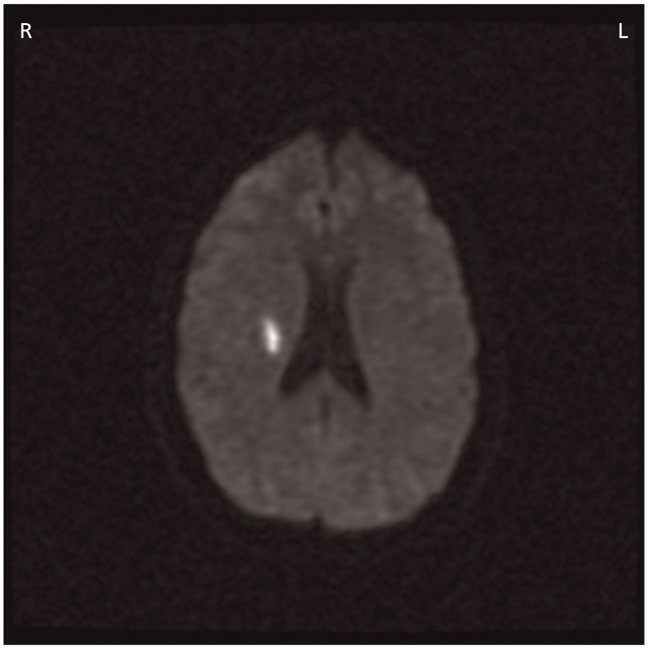

Figure 4.7 Lacunar infarction (diffusion weighted MRI).

Table 4.10 Common lacunar syndromes.

Pure motor
Sensorimotor
Pure sensory
Ataxic hemiparesis
Dysarthria/clumsy hand

The principal clinical feature of lacunar infarction is that patients lack cortical signs. Cortical signs include dysphasia, neglect syndrome, apraxia, hemianopia and conjugate eye deviation. It is difficult to tell clinically whether infarction has taken place affecting deep hemisphere structures or brainstem structures as the syndromes overlap. One is tempted to think that a profoundly dysarthric patient must have had brainstem infarction but this is unreliable. There are many lacunar syndromes but those commonly seen in practice are pure motor hemiparesis, pure sensory hemiparesis, sensorimotor hemiparesis, ataxic hemiparesis and clumsy hand-dysarthria syndrome (Table 4.10).

CT may not detect some smaller lacunar infarcts especially in the brainstem; MRI is much more sensitive. Often patients with lacunar infarction may have widespread changes and it can be difficult clinically to identify the symptomatic lesion. Appropriate patients should also have evaluation of the extracranial carotids, looking for significant stenosis. The large carotid endarterectomy trials have shown that carotid stenosis is a risk factor for lacunar

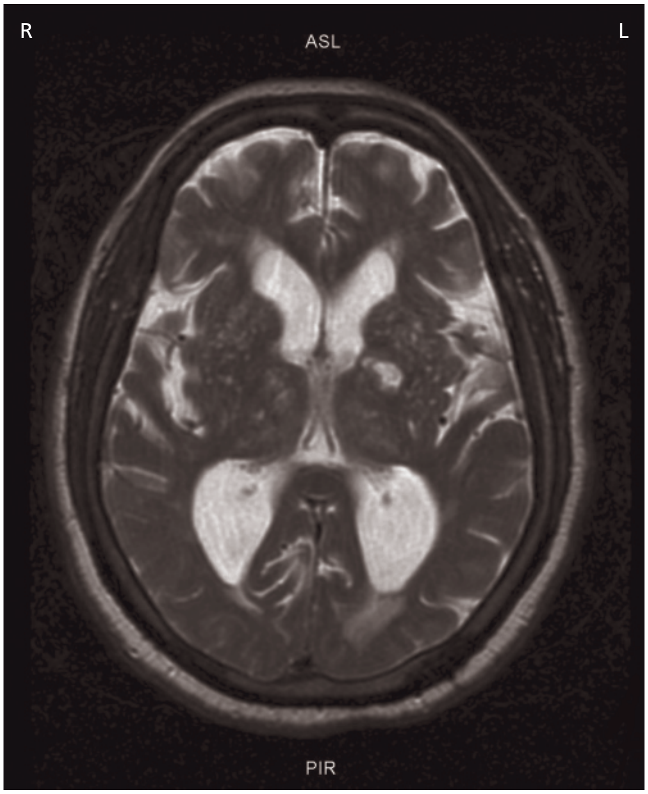

Figure 4.8 Diffuse small vessel disease (MRI T2W).

stroke. Those with severe carotid stenosis benefit from endarterectomy, in terms of secondary prevention but less than those with other syndromes. The mainstay of secondary prevention is control of hypertension, diabetes, antiplatelet agents and statins where appropriate.

If sufficient damage from repeated penetrating vessel occlusion takes place, global problems appear. These patients often have diffuse peri-ventricular change on CT and MR imaging, known as leuco-araiosis (Figure 4.8) and atrophy. They may develop gait apraxia (gait ignition failure, marche à petit pas) and postural instability with a predisposition to falling backwards, and dementia of a subcortical type with prominent lack of initiation and poor attention. Patients with small vessel disease may also be at greater risk of Alzheimer's disease (Chapter 7) and the two often coexist. These syndromes are distinct from multiple cortical stroke. Leuco-araiosis can also be found coincidently without overt symptoms or signs in those over 50 years especially with appropriate risk factors. There is an increased incidence of depression and subclinical cognitive impairment in these patients.

Rarer causes of lacunar syndromes

APAS can present with lacunar infarction; often these patients also have a history of migrainous phenomena and headaches. Anticoagulation may be needed. CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy) presents in a similar fashion (see below, and Chapter 25).

Large vessel occlusion

The pattern of infarction after large vessel occlusion will depend on many factors. The common risk factors listed above are important, but compared to lacunar infarction the emphasis skews towards large vessel stenosis and heart disease as sources of embolism.

The main clinical distinction between large vessel occlusion and lacunar infarction in the carotid circulation is the presence of cortical signs (eye deviation, dysphasia, neglect syndromes, hemianopia). The hemiparesis produced by MCA occlusion affects the arm more than the leg because of cortical involvement (the leg cortex is in anterior cerebral artery territory).

Internal carotid artery disease

The major cause of this is atherosclerosis, with stenosis in the distal common carotid artery extending to the proximal ICA and external carotid artery. Occlusive disease of other arteries commonly accompanies ICA stenosis; coexisting myocardial ischaemia and limb ischaemia are common. Atherosclerosis in the ICA produces its symptoms either by embolism, thrombus formed on ulcerated plaque, haemodynamic failure from severe stenosis (>95%) or occlusion.

An important clue to a potential ICA stenosis is transient monocular blindness, amaurosis fugax (the ophthalmic artery is the first branch above the ICA origin). Occasionally, the patient may develop a low flow retinopathy or global ischaemic ocular syndrome from a combination of small vessel and critical ICA stenosis. This may cause haemodynamic retinal symptoms including bleaching out of colours in sunlight and persistent after images from bright lights. Although a bruit may mark the presence of ICA stenosis and is an independent risk factor for stroke, the ICA flow can be so severely diminished that a bruit is absent. Embolism is most likely to produce a partial or complete MCA syndrome and is discussed below. Haemodynamic failure above a critical stenosis can lead to border-zone infarction. Horner's syndrome may be present when the artery is acutely thrombosed. Carotid occlusion occasionally presents with a stuttering deficit sometimes over many weeks.

Narrowing and thrombotic occlusion of the carotid siphon in the distal ICA is less frequent than at the origin but is usually caused by atherosclerosis. This may be more common in the Asian population. In younger patients, distal stenosis and occlusion may be caused by vasculitis, dissection or Moyamoya disease.

Middle cerebral artery occlusion

Total MCA occlusion

The MCA may be affected by embolism or thrombosis *in situ*. Patients with severe intracranial atherosclerosis have a high incidence of stroke because of thrombosis *en plaque*. People of Asian and African descent seem particularly affected by intracranial stenosis. In Caucasians, while MCA occlusion is common, MCA stenosis is rare.

If the main trunk occludes and there are inadequate collaterals then the whole territory infarcts (Figure 4.9). The clinical picture produced is sometimes known as 'front-to-back' infarction with conjugate eye deviation (frontal lobe damage), aphasia (dominant hemisphere), hemiplegia, hemisensory loss and hemianopia (parietal and temporal lobe damage). Neglect syndromes where the patient is unaware of the hemiplegic side occur acutely with both non-dominant and dominant hemisphere damage but generally only persist with non-dominant damage. Patients with complete MCA syndromes occasionally develop fatal brain swelling (malignant MCA oedema) within 48 hours of onset, leading to death from coning. In appropriate cases surgical decompression is required (Figure 4.10).

MCA branch occlusions

These produce fragments of the syndromes described above. Upper branch occlusion affecting frontal structures produces hemiparesis, hemisensory loss, ocular deviation and non-fluent motor dysphasia (expressive) where the patient understands (intact temporal lobe) but cannot produce speech. Lower branch occlusions can affect the temporal lobe resulting in fluent dysphasia (receptive) where production of speech is good but incoherant and the patient does not understand.

MCA distal embolism

Small cortical branches occluded, e.g. by emboli, may present only with weakness or isolated cortical signs, difficult to distinguish from the effects of a lacunar infarct.

MCA deep infarction (striato-capsular infarction)

This tends to occur when collateral circulation protects the cortex but deeper structures (the striatum and capsule) become infarcted (Figure 4.11). This pattern of infarction is also seen with MCA stenosis and when emboli obstruct the lenticulo-striate perforators and then break up. Patients have unilateral motor and

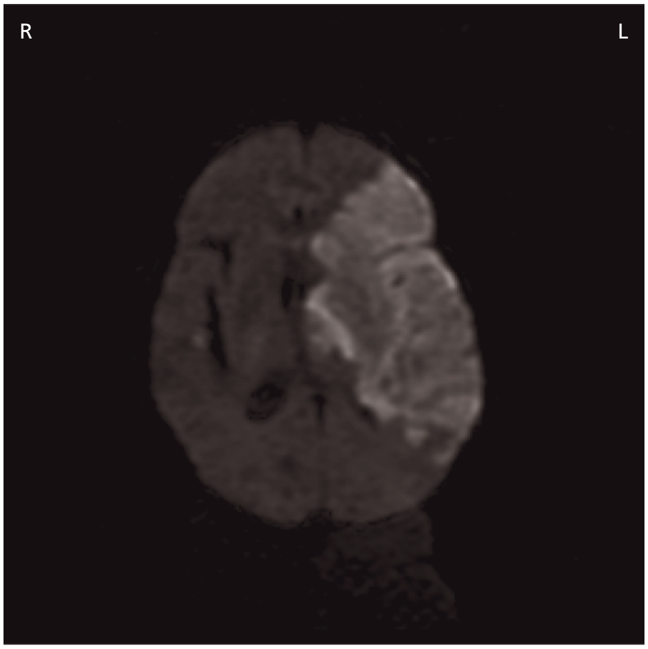

Figure 4.9 Complete MCA territory infarction (diffusion weighted MRI).

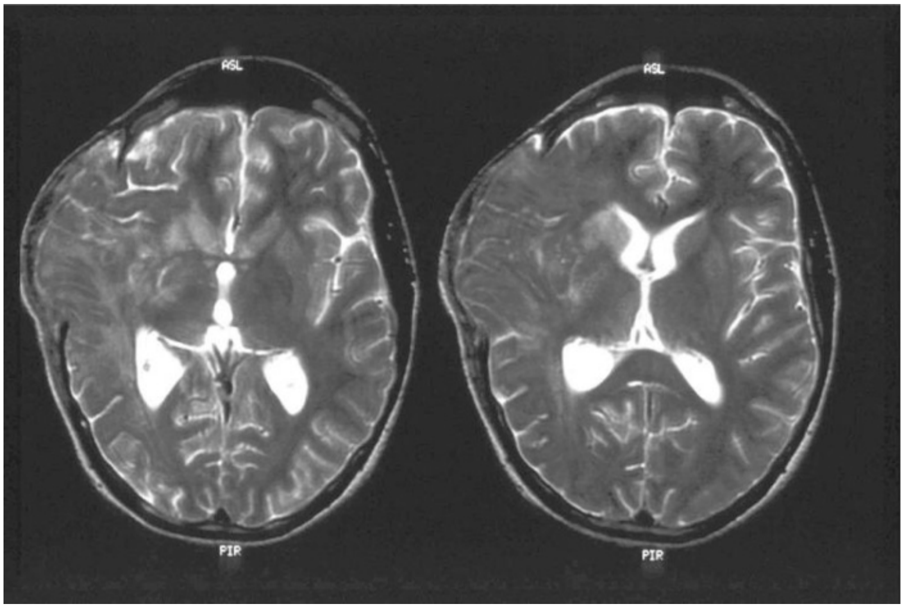

Figure 4.10 Malignant right hemisphere swelling relieved by surgical decompression following complete MCA territory infarction (MRI T2W).

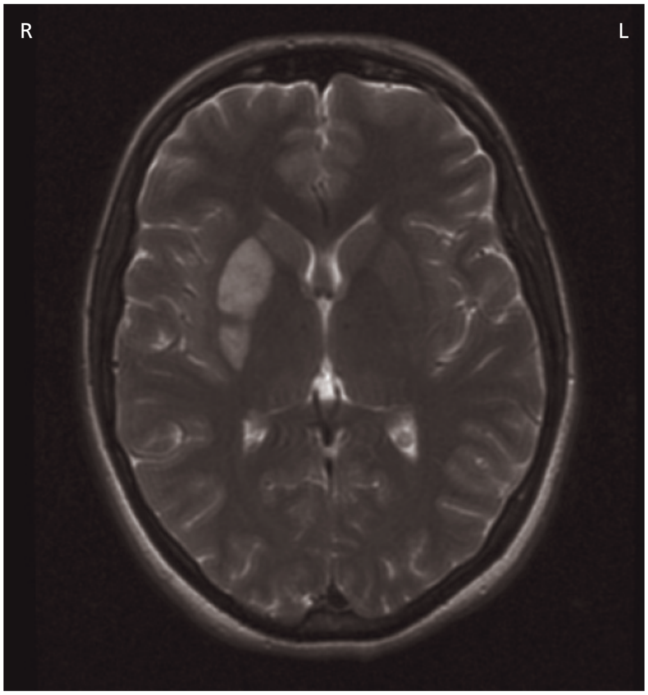

Figure 4.11 Striato-capsular infarction (MRI T2W).

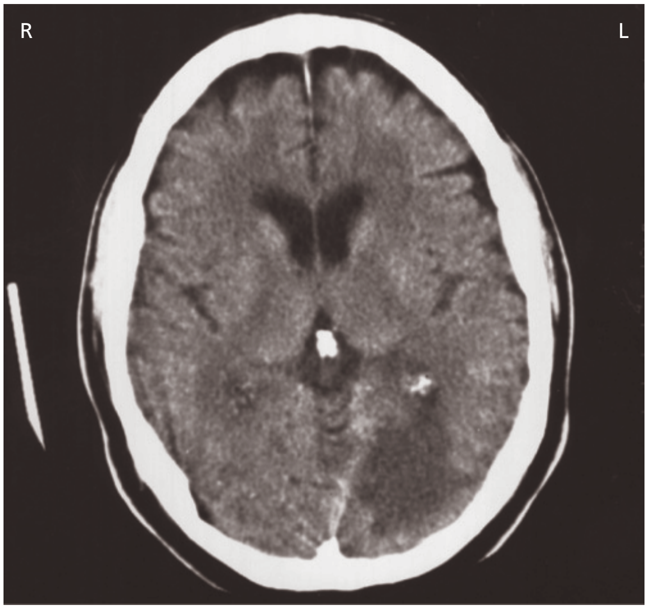

Figure 4.12 Infarction following posterior cerebral artery occlusion (unenhanced CT).

sensory loss but also exhibit cortical signs (unlike pure lacunar infarction). These cortical signs resolve more quickly than when the cortex itself is damaged. Striato-capsular infarction should prompt a search for cardiac and ipsilateral carotid sources of embolism.

Anterior cerebral artery occlusion

This territory is far less often affected than that of the MCA. Although the same risk factors apply, ACA territory infarction should raise the level of awareness for unusual aetiologies at play. This also occurs in the setting of SAH, secondary to vasospasm. The clinical features of ACA occlusion are contralateral hemiplegia. The leg is most affected as the cortical representation of the leg lies within the territory. Some patients may have motor neglect and apraxia.

Anterior choroidal artery occlusion

Syndromes include hemiparesis (face, arm and leg), prominent hemisensory loss and hemianopia, often temporary. However, unlike hemianopia associated with complete MCA infarction, other cortical signs may be subtle and transient.

Posterior cerebral artery

Occlusion of these arteries is commonly embolic. More patients with posterior cerebral artery syndromes are in atrial fibrillation than with other large vessel occlusions (Figure 4.12). The posterior cerebral artery (PCA) supplies principally the occipital cortex: an isolated hemianopia is common. When infarction is more anterior, affecting parieto-occipital areas, neglect syndromes may accompany the hemianopia. The PCAs also supply the thalami and posterior-medial temporal lobes. If these structures are involved the patient may present with confusion, dysphasia (thalamic) or memory impairment (thalamic or temporal). If both PCA territories are infarcted, as may happen when an embolus lodges at the top of the basilar, cortical blindness and confusion ensues. Sometimes, these patients may be left with tunnel vision and may recognize small but not large objects. Memory impairment, especially for new information, may be severe.

Vertebral artery

The most common pattern produced by occlusion of or embolism from the vertebral arteries is infarction of the dorsolateral medulla within the territory of the posterior inferior cerebellar artery causing a lateral medullary syndrome (Wallenberg's syndrome). This results in a Horner's syndrome, dissociated (temperature and pain) sensory loss on the ipsilateral side of the face and the opposite side of the body, nystagmus, ataxia of the ipsilateral limbs, and ipsilateral palatal and vocal cord paralysis. Vertebral embolism or occlusion may also result in more extensive infarction of the brainstem and cerebellum; these syndromes are discussed next. The most common site for atheroma to affect the vertebral artery is at its origin from the subclavian.

Basilar artery

Whereas the middle and posterior cerebral arteries are more often affected by embolism than *in situ* thrombosis, the opposite is true of the basilar artery. This is because the basilar is wider than its two feeding vertebral arteries and it can be affected by severe

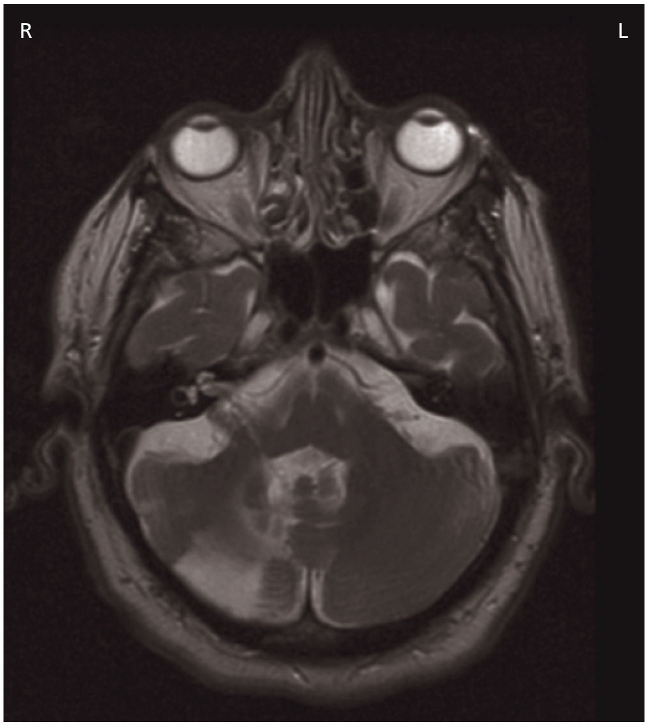

Figure 4.13 Brainstem and cerebellar infarction (MRI T2W).

atherosclerosis on which *in situ* thrombus can form (Figure 4.13). This may obstruct blood flow into perforating vessels supplying the central brainstem structures or the two upper cerebellar arteries. A number of clinical pictures may be encountered. In the medulla, lower cranial nuclei may be affected giving rise to a lower motor neurone type bulbar palsy. Upper motor neurone impairment of the same structure may cause a pseudobulbar palsy, with brisk facial reflexes, brisk jaw jerk and a spastic tongue. This is often accompanied by spontaneous laughter or crying (emotional lability). Above the medulla, pontine infarction can cause a VIth nerve palsy, gaze paresis, internuclear ophthalmoplegia and pinpoint pupils. Emboli may also lodge at the top of the basilar causing midbrain infarction with loss of vertical eye movement, pupillary abnormalities, coma or locked-in syndrome. Involvement of the origin of one or both of the posterior cerebral arteries may lead to a hemianopia or cortical blindness. All these syndromes will be accompanied by quadriparesis to some degree, which may be very asymmetric.

Watershed syndromes and ischaemic encephalopathy

The brain is particularly vulnerable to a global decrease in perfusion. Most frequently, this is caused by cardiac disease (arrhythmia or pump failure) and hypoxaemia, although hypovolaemia alone may result in these syndromes. Hypoxia without ischaemia (i.e. without reduction in blood flow) does not lead to cerebral infarction. The usual circumstance in which these patients are encountered is following cardiac arrest, severe blood loss and cardiopulmonary bypass in which embolism may also occur. Acutely in the non-anaesthetized non-comatose patient, global perfusion failure results in non-focal brain dysfunction (confusion, attentional deficits, light-headedness). Following a profound insult a number of watershed syndromes brought about by damage to the border-zone regions are recognized.

The area particularly vulnerable to reduction in perfusion pressure is the parieto-occipital cortex that lies at the superficial border-zone between MCA and PCA territories. This is the area furthest from the heart. Infarction of this region results in abnormalities of behaviour, memory and vision. The visual abnormalities are complex and include inability to see all the objects in a field of vision, incoordination of hand and eye movement such that the patient cannot locate objects in the visual field, and apraxia of gaze in which the patient cannot gaze where desired. Other areas of vulnerability are the deep border-zones within the subcortical white matter of the centrum semi-ovale, and border-zones between the ACA and MCA, and the hippocampi, where infarction may result in a Korsakoff-type syndrome. In severe cases, necrosis can follow within the basal ganglia, cerebellum and brainstem.

Vascular dementia

Dementia (i.e. cognitive deficits in multiple domains) can follow multiple cortical or subcortical lacunar infarcts (multi-infarct dementia). Typically, patients have a stepwise deterioration associated with other features of stroke. In diffuse small vessel disease, the onset may be more subtle with the more gradual onset of cognitive impairment (Chapter 7) often accompanied by gait apraxia where patients exhibit failure to initiate gait, postural instability (often falling over backwards) and a shuffling small-stepped gait. Patients with diffuse small vessel disease may have prominent attentional difficulties in excess of discrete cortical patterns of dysfunction and often present with periods of encephalopathy associated with new infarction. Multiple cortical infarcts, from large vessel occlusions, are much rarer as a cause of dementia. In addition, it is important to note that patients with vascular disease (clinically and radiologically) are at an increased risk of Alzheimer's disease and it is the latter that causes dementia in many patients with vascular disease (mixed dementia). This can be distinguished to some extent on clinical and neuropsychological grounds.

Intracranial haemorrhage

Intracranial haemorrhage may be intracerebral, within the cerebellum or brainstem (infratentorial), subarachnoid, subdural or extradural. This section deals principally with intracerebral haemorrhage (ICH) and infratentorial haemorrhage.

Approximately 10% of stroke is caused by brain haemorrhage with an annual incidence of 10–15/100,000 population. The incidence increases significantly after the age of 55 years and doubles with each decade to the age of 80. However, there has been a small but progressive decline in the incidence of both stroke and brain haemorrhage, particularly in the last three decades, because of an improvement in the management of risk factors and secondary prevention; the control of hypertension in primary care has been of particular importance.

Despite being less common than ischaemic stroke, haemorrhage has a significant impact because the subsequent mortality is so high. In one study of over 1000 stroke cases, 30-day mortality for supratentorial and infratentorial ischaemic stroke was 15% and 18%, respectively. Mortality following supratentorial and infratentorial haemorrhage was 58% and 31%. Mortality rates of 90% following brain haemorrhage have been reported.

Spontaneous ICH results from intracerebral arterial rupture, particularly perforating vessels, or less frequently from the venous system. The haematoma expands following the path of least resistance, usually along white matter tracts, and occasionally into the ventricular system. Neurological deficit results both from direct tissue destruction and indirectly from local compression and mass effect, usually in proportion to both the volume of haematoma and its rate of expansion. Intraparenchymal haemorrhage can occur at any site, although some areas are more susceptible than others. Eighty per cent of such intraparenchymal haemorrhages occur within the cerebral hemispheres and some 20% are infratentorial.

Traditionally, brain haemorrhage has been thought to have a sudden devastating presentation. While it is true that patients who present in coma following vomiting, headache and neck stiffness are more likely to have had a haemorrhage than ischaemic event, it is wrong to believe that patients with less severe stroke syndromes can be diagnosed on clinical grounds to have had ischaemic strokes. This is particularly illustrated by the recognition of microhaemorrhage with T2* imaging which occasionally reveals minute bleeds as the underlying cause of clinical syndromes previously thought to have been caused by ischaemia.

Risk factors

The most important risk factor associated with brain haemorrhage is hypertension, found in 40–60% of patients. Compared with brain haemorrhages from other causes, this type of bleed is more frequently fatal, a reflection of both its high incidence and its tendency to occur in critical locations. Hypertensive bleeds occur in deep white matter (36%), pons (11%) and cerebellum (8%), regions that are supplied by the lenticulo-striate branches of the MCA or the paramedian perforating branches of the basilar artery. The underlying weakness of these vessels is caused by hyaline degeneration of arterioles promoted by long-standing hypertension. Identical pathology can be seen in elderly patients without known hypertension.

Other conditions important in the aetiology of brain haemorrhage are aneurysms (20%), vascular malformations (5–7%), coagulopathies (5–7%), tumours (1–11%), sporadic cerebral amyloid angiopathy and haemorrhagic infarction (Table 4.11). Non-medicinal use of cocaine and amphetamines may cause haemorrhage, although there is often an underlying vascular malformation in these cases.

Table 4.11 Causes of brain haemorrhage.

- Hypertension
- Anticoagulants
- Amyloid angiopathy
- Arteriovenous malformations
- Aneurysms
- Cavernous haemangiomas
- Amphetamine/cocaine ingestion
- Infective endocarditis
- Tumours
- Disseminated intravascular coagulation
- Venous thrombosis
- Cerebral vasculitis, malaria

Aneurysms are saccular or fusiform arterial deformities, the result of protrusion of the intima through a structural defect in the arterial muscular layer. Typical circle of Willis aneurysms, also known as berry aneurysms, most commonly cause SAH, although this is associated with intraparenchymal bleeding in 30% of patients. Mycotic aneurysms usually form in smaller cortical arteries when septic emboli lodge in the vessel. This is usually seen in the context of infective endocarditis, where up to 17% of patients develop cerebral emboli. Usually, these mycotic aneurysms thrombose, if the infection is treated adequately, and no further intervention is required. Rarely, the mycotic aneurysm continues to enlarge or ruptures; surgical intervention is necessary to clip and/or resect it. Arterial invasion by tumour or severe atherosclerosis occasionally lead to aneurysm formation, although rupture is rare. Other vascular malformations that cause brain haemorrhage include arteriovenous malformations (AVMs), cavernous malformations and capillary telangiectasia. Developmental purely venous anomalies were also thought to cause haemorrhage: current understanding is that it is the cavernous malformation commonly associated with the venous anomaly that is the source of bleeding.

One of the most important and potentially treatable causes is anticoagulation, especially when poorly controlled and combined with other risk factors. Any patients on anticoagulants with new focal neurology must be assumed to have bled until proven otherwise with urgent cranial imaging. In those that have bled, anticoagulation should be immediately reversed. Other causes of coagulopathy, including thrombocytopaenia, leukaemia and liver and renal failure, may also cause similar problems. Patients with coagulopathy are also much more likely to bleed into cerebral infarcts.

Cerebral amyloid angiopathy, characterized by deposition of amyloid in the media and adventitia of medium-sized hemispheric vessels, is an important cause of recurrent or multiple superficial haematomas in elderly patients, particularly when there is no history of hypertension. It is estimated that during the seventh decade of life, 10% of the population develops amyloid angiopathy, increasing to 60% by the age of 90 years. There is a strong association with Alzheimer's disease.

Clinical syndromes

The rupture of a vessel or microaneurysm results in the sudden development of haematoma, of variable size. These haematomas characteristically then slowly enlarge, sometimes over a matter of days, leading to progressive focal neurological deficit and then deterioration of conscious level secondary to mass effect. Haemorrhage may be divided into a number of categories depending on location. These are deep (centred on basal ganglia structures), lobar, pontine and cerebellar. In all sites hypertension remains the most important risk factor and while amyloid angiopathy classically gives rise to lobar and not deep haemorrhage, hypertension is still the most important risk factor in lobar haemorrhage.

Deep haemorrhage

Haematomas may be centred on the putamen, caudate or thalamus. In putaminal haemorrhage the picture is of contralateral hemiparesis and conjugate deviation of the eyes towards the side of the haematoma (Figure 4.14). Cortical function may be impaired. If the mass becomes critical then signs of herniation ensue. These haematomas may rupture into the ventricles leading to intraventricular haemorrhage. In the case of putaminal haemorrhage the presence of ventricular blood implies a very large haematoma with a poor prognosis. Caudate haemorrhage is much rarer and small haematomas may readily rupture into the ventricles. When the lesion is large the picture is similar to putaminal haemorrhage but if small, haematomas may mimic subarachnoid haemorrhage with acute headache and meningism with little in the way of focal signs. Thalamic haemorrhage predominantly produces sensory change in the contralateral limbs. If local midbrain compression occurs the eyes may be forced into downward gaze with small poorly reactive pupils. Thalamic haemorrhage in the dominant hemisphere may produce dysphasia with notable naming difficulties.

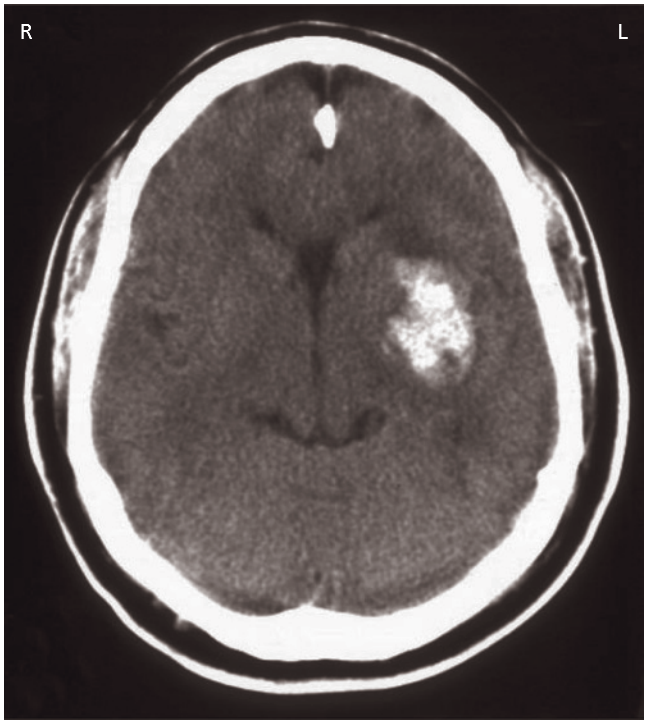

Figure 4.14 Large putaminal haematoma (unenhanced CT).

Lobar haemorrhage

These cortical lesions produce signs appropriate to their location. In the frontal lobe, eye deviation and contralateral hemiparesis is common. In the posterior frontal and fronto-parietal region, hemisensory loss is found, associated with dysphasia when the lesion is within the dominant hemisphere. Parietal lobe haemorrhage causes hemisensory loss and neglect/inattention syndromes. Bleeding into the dominant temporal lobe results in a fluent dysphasia with poor comprehension secondary to damage to Wernicke's area.

Lobar haemorrhages are more likely to be associated with structural abnormalities, e.g. a vascular malformation, than deep haemorrhages. Alternatively, amyloid, trauma, haemorrhagic transformation of infarction and a haemorrhagic tumour should be considered within the differential.

Infratentorial haemorrhage

The classic picture in pontine haemorrhage is coma associated with pinpoint pupils, loss of horizontal eye movements and quadriparesis. Hyperpyrexia and irregular respiratory patterns ensue. Although a large haematoma here is often fatal, the outcome may be surprisingly good.

Cerebellar haemorrhage accounts for some 10% of all brain haemorrhages. It is important to recognize as it may result in secondary fatal brainstem compression and hydrocephalus. Posterior fossa craniectomy to decompress the brainstem can be life-saving and patients may make an excellent functional recovery. The usual picture is of acute headache and vomiting with unilateral ataxia. Unilateral gaze paresis in association with ataxia or in isolation may occur and also skew deviation. When brainstem compression is present from the onset or develops later, the picture suggests a pontine haemorrhage, with the patient either presenting or deteriorating into coma. Emergency CT scanning is essential.

Intraventricular haemorrhage

This mimics SAH (see below) with headache, vomiting, neck stiffness and depression of consciousness. There may be associated pyramidal signs, particularly if associated with a parenchymal haematoma. This may be caused by extension of blood following deep haemorrhage, aneurysmal rupture or a subependymal angioma. This is particularly the case with caudate haemorrhage as this nucleus lies adjacent to the ventricular margin.

Specific issues in intracerebral haemorrhage

Brain imaging is mandatory, without delay. Although MRI is greatly superior to CT at refining the pathophysiological diagnosis, it is not currently available for most patients in the emergency situation. The appearances of haemorrhage on CT are also easier to interpret than on MRI, especially in non-expert hands and CT is therefore often the preferred imaging technique at presentation. Acutely, a CT is essential to distinguish infarction from haemorrhage or reveal mimics of the stroke syndrome such as tumour or subdural haematoma. Haemorrhages seen on MRI undergo complex changes depending on the image sequence, the proportion of oxyhaemoglobin, deoxyhaemoglobin and methaemoglobin, and its distribution; this may make interpretation difficult. However, signal loss on gradient echo MRI is more specific and sensitive to new and old haemorrhages than the older MRI sequences.

In appropriate patients it is necessary to exclude underlying vascular malformations with angiography. If performed in the acute situation, consideration should be given to repeating angiography once the mass effect of the haematoma has resolved. In 10% of cases where initial angiography is normal, a small arteriovenous malformation is demonstrated on delayed imaging. This is caused by occlusion of the arteriovenous malformation by the mass effect of the acute haematoma. In this situation either the angiogram should be delayed or repeated following resolution of the haematoma. MRI is often a useful complementary investigation in order to exclude underlying parenchymal lesions. Again this is best performed after some days once there has been resolution of some of the blood products.

Following a brain haemorrhage, the general supportive management issues are just as important as in ischaemic stroke. Medical treatment is aimed at correcting any underlying systemic disorder such as severe hypertension or coagulopathy, as well as preventing or limiting secondary complications such as pulmonary emboli, myocardial infarction and pneumonia. Aspirin (often taken as an over-the-counter preparation) should be stopped. Until recently, there were no specific drugs that had been shown to alter outcome. Initial trials of recombinant activated factor VII showed that this pro-coagulant appeared to reduce haematoma size and improves outcome when given within 4 hours of onset; however, phase IIb/IIIa studies have been negative. Further trials are needed to explore these findings. Frequent neurological assessments, as well as serial CT scans, are necessary particularly early in the clinical course when management can be modified accordingly.

Anticoagulant related haematomas often present as slowly evolving lesions. It is essential, even if they are small at initial imaging, to reverse warfarin immediately as delay may have devastating consequences. This maxim includes patients with prosthetic valves as the risk–benefit ratio is much in favour of anticoagulation reversal for a period of 2 weeks, after which the rebleeding rate is considerably lower. The rate of systemic embolism from thrombus on the prosthetic valve during this period is small.

Neurosurgical practice in relation to evacuating intracerebral haematomas varies. The middle of the road approach that the authors follow is to evacuate life-threatening cerebellar haematomas large enough to cause brainstem compression and hydrocephalus and superficial lobar haematomas that are causing marked mass effect. Few neurosurgeons will tackle deep-seated basal ganglia haematomas unless under exceptional circumstances, in the main because the associated morbidity is significant. The optimal management of this form of stroke beyond organized care is unclear from the evidence and the results of the recent Surgical Trial in Intracerebral Haemorrhage (STICH) suggested no significant benefit to surgical evacuation. In this prospective randomized study of over 1000 patients, there was no overall benefit from early surgery when compared with initial conservative management.

Prognosis

The prognosis of brain haemorrhage depends primarily on the location and size of the haematoma. These factors are closely followed by the patient's age, the cause of the haemorrhage and the development and severity of post-haemorrhagic complications such as cerebral oedema, hydrocephalus and raised intracranial pressure, as well as systemic complications such as pulmonary embolus, MI and pneumonia. In gauging prognosis and discussing possible outcome with a patient or their relatives, it is worth pointing out that improvement following haemorrhage tends to be more delayed than following infarction, and that there are some cases where eventual recovery is good following resolution of the haematoma.

Subarachnoid haemorrhage

The main cause of non-traumatic SAH is rupture of an intracranial aneurysm. This accounts for 85% of cases. SAH is a devastating condition with an overall case fatality of 50% (including pre-hospital deaths), with 30% of survivors being left dependant, with major neurological deficits. In spite of many advances in diagnosis and treatment over the last decades, the case fatality rate has changed little, if at all.

Non-aneurysmal peri-mesencephalic haemorrhage is seen in 10% of cases and carries a good prognosis with less frequent neurological complications. The remaining 5% of cases are caused by rare conditions, including AVMs (including spinal AVMs), cerebral vasculitides, tumours, dural arteriovenous fistula, dural sinus thrombosis, carotid or vertebral artery dissections, coagulopathy and drugs.

The annual incidence of SAH in UK is approximately 10/100,000, increasing consistently with age until the sixth decade, with a peak incidence at 55–60 years. There are marked variations in the incidence of SAH worldwide. The incidence is lowest in the Middle East and highest in Japan, Australia and Scandinavia, especially in Finland where SAH incidence is around three times that of the rest of the world. The age-specific rates for SAH tend to be higher in those of Afro-Caribbean origin than Caucasian. There is female preponderance, with male : female ratio as around 1 : 1.8.

Risk factors

The risk of aneurysmal rupture depends on the size and location of aneurysm. The International Study of Unruptured Intracranial Aneurysms (ISUIA) documented a 5-year cumulative rupture rate for all aneurysms of the anterior circulation (except posterior communicating [PCOM] artery aneurysms) of 0%, 2.6%, 14.5% and 40% if sized less than 7, 7–12, 13–24 and more than 25 mm, respectively. The same risks for posterior circulation and PCOM artery aneurysms were 2.5%, 14.5%, 18.4% and 50%, respectively.

Most cases of aneurysmal SAH are sporadic; however, there is considerable evidence to support the role of genetic factors in the development of intracranial aneurysms. There is a strong association between intracranial aneurysms and heritable connective tissue diseases, although these form a small proportion of any case load of the order of 5%. These conditions include autosomal dominant polycystic kidney disease, Marfan's syndrome, pseudoxanthoma elasticum, Ehlers–Danlos syndrome and α_1-antitrypsin deficiency. Familial intracranial aneurysms account for 7–20% of patients with aneurysmal SAH. Approximately one-third of asymptomatic members of affected families will have evidence of intracranial aneurysms on angiography. In one study of 8680 individuals, the prevalence of asymptomatic aneurysms in the subgroups with and without a family history was 10.5% and 6.8%, respectively. The relative risk of siblings of SAH patients having a haemorrhage is six times that of the general population, with a threefold increased risk in parents – an overall fourfold increased risk in first degree relatives. Familial aneurysms tend to rupture at a smaller size than sporadic cases and often display genetic anticipation, with haemorrhages occurring at progressively younger ages in successive generations. The occurrence of aneurysms at identical and/or mirror sites is more frequent in familial cases and appears to be a function of the degree of kinship between affected individuals.

Environmental factors have been extensively studied and cigarette smoking is the only factor consistently identified, raising the risk 3–10 times that of non-smokers. This also appears to be a dose-dependent effect. The SAH risk decreases with the number of years since giving up smoking, with excess risk largely disappearing 2–4 years after cessation of smoking. Hypertension is almost certainly important but to a lesser degree, although there is conflicting evidence over its role as it is a common co-morbid condition. It seems that hypertension and smoking act as synergistic risk factors. The risk of SAH in hypertensive smokers is nearly 15 times that in the non-smoking non-hypertensive population. There is a strong temporal association between snorting cocaine (and other methods of ingestion) and both haemorrhagic and ischaemic cerebrovascular events. The use of sympathomimetic drugs, such as cocaine and methamphetamine, tend to increase the incidence and decrease the age at which aneurysmal rupture occurs; aneurysmal size at rupture also tends to be smaller.

Clinical features

The cardinal clinical feature is the sudden onset of a thunderclap headache. Headache is present in the majority of patients. This is usually of unique severity and sudden onset and is often accompanied by nausea and vomiting (77%). Thunderclap headache, although a cardinal feature, is non-specific and only 1 in 10 of those presenting with a sudden explosive headache will turn out to have had an SAH. There are no highly reliable features from the history that distinguish benign thunderclap headache from SAH. Exceptionally, bacterial meningitis can present with SAH.

Signs of global or focal dysfunction may be found depending on the severity and location of SAH. Consciousness is frequently altered, with confusion and lethargy in 30%, transient loss of consciousness in one-third and coma in 17%. In these patients, a history of headache may be lacking. Signs of meningeal irritation are found in most but not all patients and it is a common error for these either not to be elicited or misinterpreted in patients with acute headache. Neurological abnormalities are seen in 64% of cases with focal signs such as hemiparesis, IIIrd or VIth nerve palsies in 21%. Focal deficits may be caused by intraparenchymal extension of blood or later by vasospasm with resultant ischaemia and infarction.

Symptoms do sometimes help to localize the aneurysm. Anterior communicating artery (ACOM) aneurysms may present with frontal symptoms (bilateral lower-limb weakness, bilateral extensor plantars, incontinence and abulia) and electrolyte disturbance is not uncommon. Both anterior choroidal (although uncommon) and MCA aneurysms may present with hemiparesis, aphasia or visuo-spatial neglect, while peri-callosal artery and distal ACA aneurysms present with a contralateral lower limb monoparesis. A IIIrd nerve palsy suggests an aneurysm of the PCOM artery (Figure 4.16), or less commonly of the superior cerebellar artery. A painful pupil-involving IIIrd nerve palsy is usually a warning of potential imminent rupture of a PCOM artery aneurysm and should be investigated without delay.

Retinal and preretinal (subhyaloid) haemorrhages are seen in 25% of SAH patients. There are three types of haemorrhage that can occur alone or in combination with SAH:

1 Retinal haemorrhages may surround the fovea;

2 Subhyaloid preretinal haemorrhages are seen in 11–33% of cases as bright-red blood near the optic disc;

3 Terson's syndrome, consisting of haemorrhage within the vitreous humour occurs in approximately 4% of SAH cases and usually bilaterally.

Subhyaloid and vitreous haemorrhages are associated with a high mortality rate. Terson's syndrome patients who survive should be followed for the long-term complications of raised intra-ocular pressure and for retinal detachment.

Many retrospective studies comment on unusual or acute headaches predating the definite SAH by several days to weeks.

These headaches have been thought to represent warning leaks, intramural haemorrhage or aneurysmal enlargement and are sometimes called sentinel headaches. This may occasionally be the case. An alternative explanation is recall bias. A prospective study examining 148 patients with sudden onset headaches of thunderclap type showed that only 25% went on to SAH. Of these SAH patients, only two could recall a similar headache previously.

SAH tends to be misdiagnosed – as migraine or benign acute headache syndrome – typically when the headache is not catastrophic in severity, but simply sudden. Some of these SAH cases remain ambulant – and in these low back pain and sciatica resulting from local irritation by blood products can develop within 4–10 days of the haemorrhage. At the other end of the spectrum a small proportion of SAH cases are found dead, or are seen to die rapidly, within minutes or hours from massive haemorrhage.

Investigation

CT is mandatory in those with suspected SAH, generally revealing diffuse blood of a symmetrical distribution around the basal cisterns, Sylvian fissures and cortical sulci (Figure 4.15). Modern generation CT will demonstrate the presence of blood in 95% of patients scanned within 48 hours. However, blood is rapidly cleared from the cerebrospinal fluid (CSF) and the CT pick-up rate gradually decreases to 80% at 3 days, 50% at 1 week and 30% at 2 weeks. When asymmetrical or localized, the distribution of blood may suggest the location of the aneurysm in up to 70%. This is particularly important in the 10–15% of patients who harbour multiple aneurysms, when it may help to guide intervention towards the aneurysm that has bled. Intraventricular haemorrhage is characteristic of ruptured ACOM artery aneurysms; intracerebral haemorrhage is most commonly seen with PCOM artery and MCA aneurysms. Head CT can also demonstrate hydrocephalus, cerebral ischaemia or infarction, midline shift or a rebleed.

If clinical suspicion is strong and the CT is normal, lumbar puncture preferably by an experienced operator should be performed assuming there are no contraindications. If clinically appropriate this should be delayed for 12 hours from the ictus to allow time for xanthochromia (yellow discoloration) to develop. Xanthochromia of the supernatant, which is positive in almost all SAH patients between 12 hours and 2 weeks, is diagnostic. This must be determined by spectrophotometry rather than visual inspection. Negative CSF is very helpful in excluding SAH but bloodstained CSF may result from a traumatic tap. A decrease in the number of red cells from bottles one to three is a very unreliable way of supporting a traumatic tap instead of SAH. It should be remembered that patients may have had both SAH and a traumatic tap.

Conventional MRI is not sensitive to acute haemorrhage as there is too little methaemoglobin for haemorrhage to be easily differentiated from CSF. Visualization of blood products by MRI improves over 4–7 days following SAH. MRI is therefore excellent for demonstrating subacute and previous SAH, when the diagnostic yield from CT falls.

In patients with either diagnostic CT and/or lumbar puncture, or when results of these tests are equivocal, some form of arterial

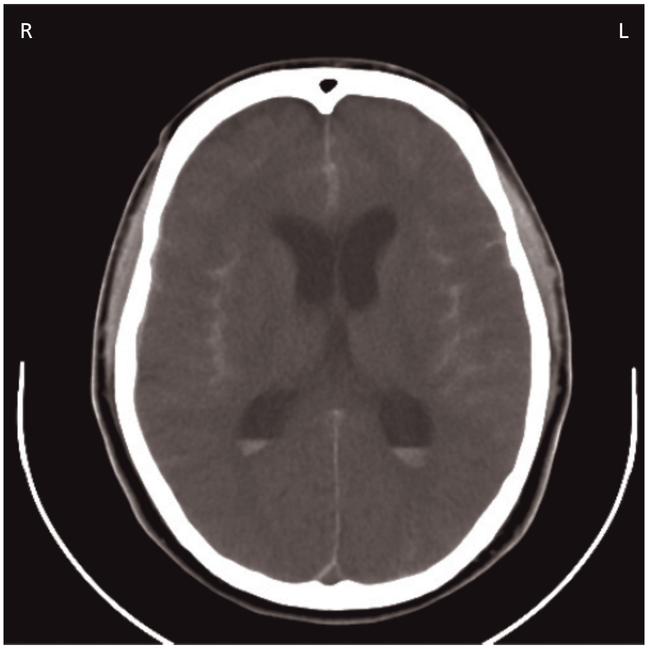

Figure 4.15 Diffuse subarachnoid and intraventricular blood (unenhanced CT).

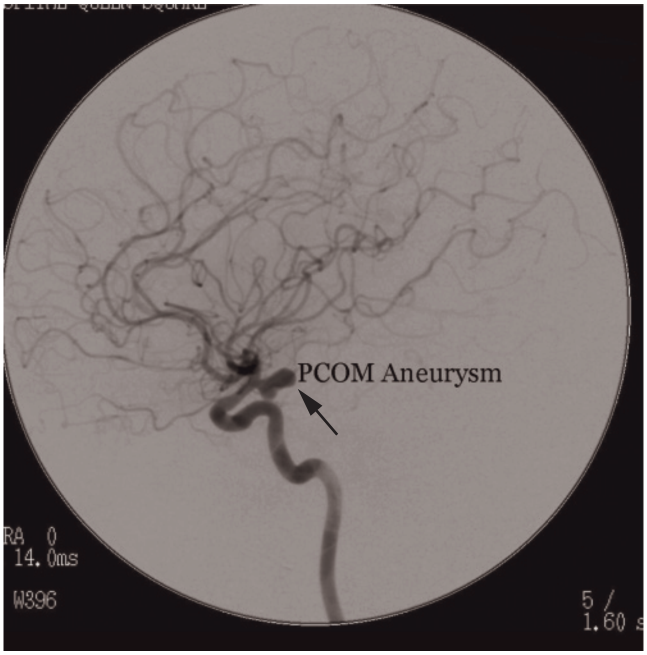

Figure 4.16 Large bi-lobed posterior communicating (PCOM) artery aneurysm (catheter angiogram).

imaging is necessary to search for a ruptured aneurysm or other lesion. Digital subtraction angiography (DSA) has been the gold standard investigation until recently, but non-invasive alternatives, including CT and MR angiography, are gaining popularity. DSA should demonstrate the aneurysmal site, type, size, orientation, neck intraluminal calcification and thrombus, the relationship between aneurysm and parent vessel, collateral flow through the circle of Willis, the presence of adjacent perforators and the state of the cerebral vasculature, including other aneurysms. In the case of multiple aneurysms, identification of the ruptured lesion may be difficult. The distribution of blood and location of any focal intraparenchymal haematoma on CT are more useful for identification. In situations where the CT reveals diffuse blood or the haemorrhage had been diagnosed on lumbar puncture, and multiple aneurysms are found subsequently, the aneurysm most likely to have ruptured is usually the largest, has greater irregularity, mass effect or associated local vasospasm.

Recent advances in three-dimensional CT angiography have meant that it now has a sensitivity and specificity approaching that of percutaneous arteriography (sensitivity 77–97% and specificity 87–100%). Imaging time is significantly reduced, allowing acquisition of the entire CT volume in 30–45 seconds during the first arterial pass of an intravenous contrast injection, with minimal patient movement artefact. Its non-invasive nature is likely to obviate the need for cerebral angiography with its inherent risks, at least as a first line investigation. MR angiography also reveals most aneurysms greater than 3 mm in diameter. The sensitivity of MR angiography for identification of aneurysms is 85–90%, with a specificity greater than 90% when compared with DSA as the gold standard, with an excellent intra-observer consistency and good-to-excellent inter-observer reproducibility. However, MRI times are significantly longer than CT. This is particularly relevant in this group of patients who are often in great pain and restless.

Despite thorough investigation, 10–15% of SAH cases have a normal angiogram. Of these, 65% will have a distinctive pattern of subarachnoid blood lying in the prepontine or perimesencephalic cisterns. These patients tend to be younger, non-hypertensive, of better clinical grade and more often male than SAH patients with angiograms positive for aneurysms. The aetiology of the SAH in these cases is unclear but the cause may be venous haemorrhage. The overall prognosis tends to be good, partly because rebleeding is rare and few patients develop delayed ischaemic deficit. However, the diagnosis should only be entertained with caution as 10% of vertebrobasilar aneurysms present with a similar distribution of blood. Repeat imaging should be considered carefully because these aneurysms can be obscured by vasospasm, hypoperfusion, poor angiographic technique or thrombosis. Such re-imaging at 2–4 weeks finds previously undetected aneurysms in 2–5% in these cases.

Initial management

General supportive care should be instituted. Stabilization of the patient, with optimization for aneurysm treatment, together with prevention of secondary cerebral insults is achieved by ensuring adequate ventilation and oxygenation, normovolaemia and haemodynamic stability and control of intracranial pressure. Frequent neurological examination is required in order to identify any neurological deterioration requiring further investigation or management.

Bed rest is generally recommended until aneurysm treatment is undertaken. Aspirin should be stopped, if it is being taken. Nimodipine, a calcium-channel antagonist has been shown to reduce the risk of cerebral infarction by 34% and as a result, poor outcome following SAH by 40%. A dosage of 60 mg 4-hourly is currently used. With a ruptured aneurysm prior to surgery or coiling, gentle volume expansion with slight haemodilution may help to return the circulating volume to normal and prevent or minimize the effects of vasospasm; however, hypertension should be avoided. Once the aneurysm has been secured, hypertension is allowed (see below), but there is no agreement on the safe range. Hyperglycaemia and hyperthermia are both associated with a poor outcome and should therefore be corrected. These problems are more often seen in poor grade patients, and their effect on outcome may therefore not be independent of presenting clinical condition. Analgesia is often required.

Aneurysm treatment

Currently, the two main treatment options for securing an aneurysm are microvascular neurosurgical clipping and endovascular coiling. Traditionally, craniotomy and clipping has been the method preferred, although the timing of surgery has been debated. The rebleeding rate from aneurysms is particularly high during the first 2 weeks, and then declines. This early high rebleed rate, which may have devastating complications, together with more recent improvements in microsurgical techniques, is the reason why early intervention is generally favoured. Securing the aneurysm will also facilitate the treatment of complications such as cerebral vasospasm. The Guglielmi Detachable Coil (GDC) has been available since 1991 and has been increasingly used in clinical practice. Detachable platinum coils are delivered endovascularly into the aneurysm. Once the correct position within the aneurysm has been achieved, the coil is detached from the wire. Multiple coils of various lengths and thicknesses are often packed into the aneurysm to exclude it from the circulation. The recently published results of the International Subarachnoid Aneurysm Trial (ISAT) suggest that patients treated by endovascular means have a 24% better chance of survival, free of disability, at 1 year than those treated surgically. The risk of epilepsy was substantially lower in patients who underwent endovascular coiling, but the risk of rebleeding was higher. Also, in patients who underwent cerebral angiography, the rate of complete occlusion of the aneurysm was greater with surgical clipping. ISAT was a landmark study that validated the technique of endovascular coiling in patients suitable for either treatment method. However, many aneurysms are not equally suitable for either microsurgical clipping or endovascular coiling. In individual cases, several factors – such as patient's age, and overall medical condition and the aneurysm's location, size, morphology and relationship to adjacent vessels – need to be analysed by a multidisciplinary team to decide on the most appropriate treatment.

Management of complications

Neurological complications are common and include symptomatic vasospasm (46%), hydrocephalus (20%) and rebleeding (7%).

Untreated, 15–20% of patients will rebleed in the first 2 weeks, carrying with it a significant mortality (50–75%) and risk of permanent neurological disability. There is an initial peak of rebleeding in the first 48 hours of approximately 4%, which rapidly plateaus to 1–2% per day until 40 days post-haemorrhage. After 6 months there is a long-term risk of further haemorrhage of 3% per year in patients whose aneurysm has not been excluded from the circulation. The risk of rebleed is increased with poor clinical grade, posterior circulation lesions, hypertension, elderly patients and abnormal clotting.

Cerebral vasospasm is multi-factorial in origin. The mechanisms include the liberation of spasmogenic metabolites during clot lysis in the basal cisterns and impairment of cerebral vasodilatation related to endothelial dysfunction and structural changes within the arterial wall. Symptomatic vasospasm, often leading to delayed ischaemic deficit, occurs in 20–30% of patients and is at its worst 3–14 days following the haemorrhage. The severity and distribution of vasospasm are related to the amount and site of subarachnoid blood. Basal subarachnoid blood tends to be a more important risk factor for vasospasm than intraventricular blood or diffuse blood over the cortex. Other predisposing factors include increasing age of the patient, high systolic blood pressure, poor clinical grade, decreased conscious level, the presence of a motor deficit or hydrocephalus, while patients with vertebral aneurysms, predominantly intraventricular haemorrhage or a negative CT, have a lower risk of developing symptomatic vasospasm. Diagnosis of vasospasm can be difficult and is often made after exclusion of other causes of neurological deterioration such as hydrocephalus, electrolyte disturbance, seizures or a rebleed. Elevated velocities on transcranial Doppler can be useful in confirming clinical suspicion. Once identified, patients are treated with hypervolaemia and induced hypertension in an attempt to improve cerebral blood flow. In those patients refractory to medical treatment, transluminal balloon angioplasty at the site of the most severe vasospasm, or vasodilator infusion (e.g. papaverine) can be used to improve both angiographic appearances and the patient's clinical condition.

Symptomatic hydrocephalus caused by diminished CSF absorption is seen in 10–35% of patients. Acutely, hydrocephalus is treated by a period of external ventricular drainage but in the longer term, 10–15% of patients will require a permanent ventriculo-peritoneal shunt.

The highest risk of seizures is within the first 24 hours of initial bleeding, occurring at presentation in 3–18% of individuals. Epilepsy persists in 6–15% of survivors and is associated with intraparenchymal haematoma, vasospasm, MCA aneurysms, poor clinical grade, systemic hypertension, peri-operative complications, rebleed, early seizures, shunt-dependent hydrocephalus, neurological deficit and blood load.

The most common medical complications of SAH include pulmonary oedema in 23% (either cardiogenic or neurogenic), cardiac arrhythmias in 35% and electrolyte disturbances in 28% of patients. Hyponatraemia (Chapters 19, 25), is caused either by cerebral salt-wasting, with low-intravascular volume, or the syndrome of inappropriate anti-diuretic hormone (SIADH), with normal or increased intravascular volume; both, if left untreated, have a high morbidity and mortality. The distinction is important because cerebral salt-wasting is treated by aggressive fluid administration and sodium supplements, while treatment of SIADH involves fluid restriction. Fluid restriction of patients with cerebral salt wasting will worsen their hypovolaemia and will predispose them to vasospasm.

Outcome

Pre-hospital mortality is 3–26%, with an overall mortality of 45–60% in the first 30 days following SAH. Overall morbidity is some 25–33%, caused in the majority of patients by vasospasm, although initial deficits and intervention also contribute. The major predictive factors for a poor outcome are level of consciousness on admission, age and amount of blood on presenting CT. More than 50% of survivors report problems with memory, mood or neuropsychological function. Despite this, half to two-thirds of patients surviving SAH are able to return to work 1 year after presentation. Prompt physical and neuropsychological assessment for rehabilitation are important.

Arteriovenous malformations

Arteriovenous malformations (AVMs) form part of the larger group of structural cerebral vascular malformations (CVMs). Also included within this group of developmental vascular anomalies of the central nervous system are cavernous malformations, developmental venous anomalies and capillary telangiectasia. AVMs are characterized by a complex tangle of abnormal arteries and veins that lack a capillary bed but are linked either by one or more direct fistulas creating an arteriovenous shunt, or through a mass of dysplastic vessels within the nidus. Although considerably less common than intracranial aneurysms, with a prevalence of 0.14–0.5%, AVMs are an important cause of haemorrhage in patients under 40 years old. They are thought to arise from developmental derangements of the cerebral vascular system during the 40–80 mm stage of embryogenesis.

Presentation

Some 65% of individuals with AVMs present with haemorrhage at a peak age of 25–40 years. These figures may under-represent the true incidence of haemorrhage as clinically silent haemorrhage is diagnosed by imaging or at surgery in as many as 10% of patients: haemosiderin staining is seen surrounding the lesion.

It has been postulated that episodes of acute headache, seizures or other acute neurological symptoms may also represent episodes of otherwise silent haemorrhages. Risk factors for haemorrhage include increasing age, previous haemorrhage (particularly in the preceding 12 months), deep site (basal ganglia and posterior fossa especially), small size, diffuse nidus, deep venous drainage, a single draining vein and associated aneurysms. Haemorrhage may be intracerebral, subarachnoid or intraventricular. Most supratentorial haemorrhages are lobar in location, but they also occur in the basal ganglia or thalamus. In the posterior fossa, AVMs are the cause of most cerebellar haemorrhages in normotensive patients less than 40 years old. Pial-based AVMs may cause direct SAH. In most instances, however, SAH results from the rupture of an intraparenchymal bleed through the pial surface. In contrast to aneurysms, SAH from an AVM is rarely associated with vasospasm and recurrent haemorrhage within the first 2 weeks of AVM rupture occurs in only 1% of patients.

Alternative presenting symptoms in patients with AVMs include seizures in 20–30%, particularly if the lesion is large, involves the cortical surface or temporal lobe or there has been previous haemorrhage or surgery. Frontal lobe AVMs commonly present with generalized seizures, motor strip AVMs can cause Jacksonian seizures and medial temporal lobe AVMs are often associated with complex partial seizures. Patients may also present with non-haemorrhagic focal neurological symptoms. Most commonly seen in lesions within the MCA distribution, the focal symptoms are dependant on the location of the AVM. Large basal ganglia lesions may present with slowly progressive dementia, hemiparesis or visual field defect, while occasionally brainstem AVMs produce motor or sensory deficit with or without cranial nerve involvement, sometimes with patterns resembling multiple sclerosis. The cause of neurological deficit is often uncertain: recurrent haemorrhages, multiple micro-infarcts, decreased perfusion because of arterial stenoses, venous hypertension and steal phenomena have all been noted as mechanisms. Patients with AVMs often complain of headaches although, as a primary presentation, they are unusual (12%). Pain tends to be well localized, unilateral and throbbing and is often difficult to distinguish from other types of vascular headache or migraine. Headaches occur more frequently in AVMs that have a significant dural or pial component and despite treatment of the lesion, they often persist following treatment. Cranial bruits are present in as many as 25% of cases and again are more common with dural AVMs. With widespread MRI, many asymptomatic AVMs are now discovered coincidentally.

Natural history

Knowledge of the natural history of a disease is a prerequisite for evaluating the influence of any treatment on the course of that disease. This is especially true when the risks of therapy may be profound. Advances in treatment for AVMs are developing more rapidly than advances in our knowledge of their natural history. It has become increasingly difficult to identify large groups of untreated patients with AVMs for prospective study because of the availability of so many treatment options. Although it is possible to quote expected mortality and morbidity figures for AVMs on the basis of size, location and angioarchitecture, estimating the risks associated with a specific AVM is much more difficult. It is therefore important that the management of any patient with an AVM should be evaluated and planned carefully by an experienced multidisciplinary team of neurosurgeons, neuroradiologists and neurologists.

The treatment of AVMs is primarily intended to eradicate or lessen the risk of future haemorrhage. Untreated AVMs do have a significant risk of mortality and morbidity, most commonly associated with haemorrhage. In one prospective study, the annual mortality rate was 1% and that of severe morbidity 1.7%, these rates being constant over some 24 years. The long-term risk of AVM rupture for patients with symptomatic AVMs is estimated to be 2–3% per year. The risk appears higher in children and probably in those patients who have had a previous haemorrhage. Factors associated with AVM haemorrhage include small size, deep location, intranidal aneurysms, deep venous drainage and draining vein stenosis. A single haemorrhage is associated with 10–13% mortality and 30% serious morbidity. There is controversy whether or not treatment of high risk components within an incurable AVM, e.g. venous aneurysms, modifies the bleeding risk.

Management

In any patient where treatment is considered, MRI and formal angiography in expert hands is performed to define this angioarchitecture and to give precise anatomical localization (Figure 4.17). This allows the risks of treatment or conservative

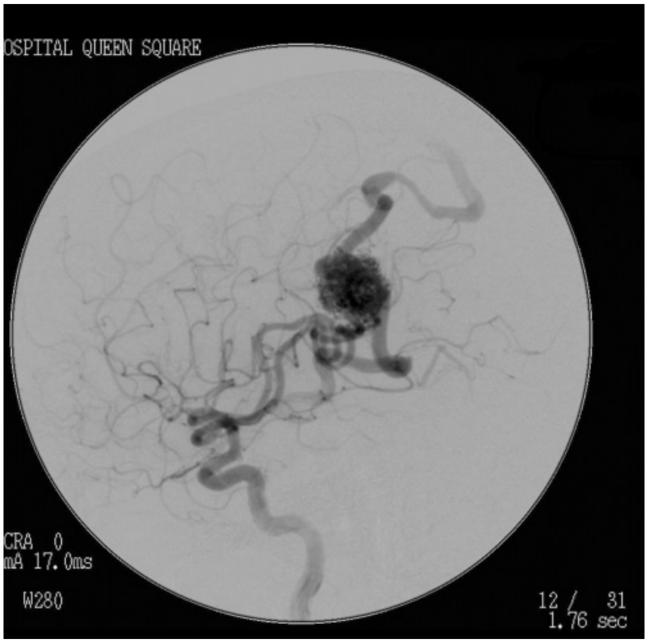

Figure 4.17 Parietal AVM (catheter angiogram).

Table 4.12 Example of surgical risks according to Spetzler–Martin grade.

Grade	No deficit (%)	Minor deficit (%)	Major deficit (%)
I	100	0	0
II	95	5	0
III	84	12	4
IV	73	20	7
V	69	19	12

management to be defined as accurately as possible. A variety of anatomical and physiological factors such as AVM size and location, number and distribution of arterial feeders, pattern of venous drainage and flow through the AVM nidus influence the technical difficulty and consequent risk of surgical, endovascular or radiosurgical treatment. The Spetzler–Martin AVM grading is commonly used (Table 4.12). This stratifies surgical risk specifically in association to the size, venous drainage and eloquence of surrounding brain and is frequently used in this decision-making process.

Many factors influence whether or how an AVM should be treated including age and co-morbidity, presentation, AVM location, size, morphology and complexity, expected natural history and treatment risks. Management plans for these lesions should only be made by a multidisciplinary team that can balance risk of treatment against expected natural history. Following rupture of an AVM, the risk of early rebleeding is significantly lower than that observed in aneurysmal rupture. Consequently, AVM treatment can be considered carefully and can often be delayed to allow the patient to recover and undergo treatment under optimal conditions.

Treatment modalities include operative resection, endo-vascular embolization and stereotactic radiosurgery, either alone or in combination. Surgical removal of an AVM is the most definitive treatment offering the best chance of lasting cure. Surgery for accessible lesions, particularly if small with single arterial supply and venous drainage, is the treatment of choice. Nevertheless, surgery carries significant mortality and morbidity. Patients should be carefully selected. Complete surgical resection should be confirmed by formal angiography postoperatively.

Endovascular embolization of AVMs is a rapidly evolving technique. The present agent of choice is *N*-butyl cyano-acrylate (NCBA). It is successful in eradicating approximately 20% of lesions. Procedural risk can be high. Between 2% and 17% have major or minor morbidity and mortality is 1–4%. The overall risk of an ischaemic complication per procedure is around 10%. Inadvertent glue deposition in normal cerebral vessels can cause infarction. Catastrophic AVM rupture from glue placement in a draining vein (raising intranidal pressure) is also a significant complication. However, endovascular treatment can be an extremely useful adjunct to surgery and radiosurgery, by reducing blood flow and eliminating surgically inaccessible arterial feeders pre-operatively. Sequential endovascular treatments can incrementally reduce the size of an AVM, making it amenable to definitive surgical or radiosurgical treatment. In some patients, endovascular treatment is useful in palliation, particularly for refractory headaches or progressive neurological deficit. However, recanalization of previously embolized segments can certainly occur in the long-term.

Stereotactic radiotherapy (Chapter 20), in particular LINAC or gamma knife radiosurgery can be used in selected patients to provide a single high dose of stereotactically localized radiation to the AVM nidus. The usual radiation dose is 20 Gy. This is administered to the margin of the nidus. This radiation causes endothelial damage, smooth muscle cell proliferation, progressive sclerosis and subsequent thrombosis of nidal vessels over time. The success of stereotactic radiosurgery depends on AVM size and radiation dose delivered. Several studies have demonstrated AVM obliteration in 80% with nidal size less than 2–3 cm diameter or 10 mL volume by 2 years. A small percentage will go on to thrombose between 24 and 36 months. The patient remains at risk of haemorrhage during this time. Delayed radiation injury, such as radiation necrosis of cortical tissue or cranial nerve palsy, is related to the radiation dose, volume treated, patient age and AVM flow characteristics. Radiation-induced tumours are very rare and generally occur many years after treatment. Radiation-related complications are correlated with the volume of normal brain tissue that receives greater than 12 Gy.

Conservative management, i.e. no intervention whatever, may be the best option in those patients with a low life-long risk of haemorrhage, e.g. asymptomatic older patients, given that all available treatment modalities have risks and the uncertainty about their benefits. Younger patients with a history of haemorrhage are now almost always offered some form of treatment. AVM cases should probably not take aspirin, nor probably non-steriodal anti-inflammatory drugs unless there is good reason.

Cavernous malformations

Cavernous malformation (CM), also called cavernous angiomas, cavernomas or cavernous haemangiomas, have a prevalence around 0.5% in the population. A retrospective review of MRI scans reported a detection rate of 0.4–0.9%. They are uncommon in children and have a peak incidence in the fourth and fifth decades of life. Overall, they account for 10% of all symptomatic intracranial vascular abnormalities. They can be familial and are often multiple.

Grossly, CMs are well-circumscribed, lobulated, raspberry-like lesions that vary from a few millimetres to several centimetres in diameter. Microscopically, they consist of a tangle of intertwined cluster of sinusoidal vascular channels that have one layer of endothelial lining and a variable layer of fibrous adventitia. Radiological evidence of previous haemorrhage, usually silent, is common, and there is often thrombosis within the dilated venules.

CMs are commonly asymptomatic but they may present with seizures or haemorrhage. Occasionally there is a progressive development of a neurological deficit, most likely to be caused by recurrent small bleeds. The frequency of haemorrhage among those who present either incidentally or with seizures is 0.4–2% per year. Among those presenting with symptomatic haemorrhage, the annual recurrent risk of haemorrhage is higher: 4–5% in the subsequent year. The risk of haemorrhage does appear to be dependent on location; there is a higher risk associated with deep lesions – brainstem, cerebellum, thalamus and basal ganglia. CMs are most readily seen on MRI as a combination of high and low T1 and T2 signal with surrounding haemosiderin (Figure 4.18). They are angiographically occult.

Surgery is usually considered in patients with multiple haemorrhagic episodes and sometimes in those with poorly controlled seizures. Most surgeons have a high threshold for advising surgery for CMs; but excision, even for those CMs in critical locations, often has an unacceptable morbidity. Radiosurgery has also been carried out but it is unclear whether it alters the natural history. The concept that CMs tend to bleed in clusters supports the decision to treat CMs with stereotactic radiosurgery. Some studies suggest a reduced haemorrhage rate, usually after a 1–3 year latent period.

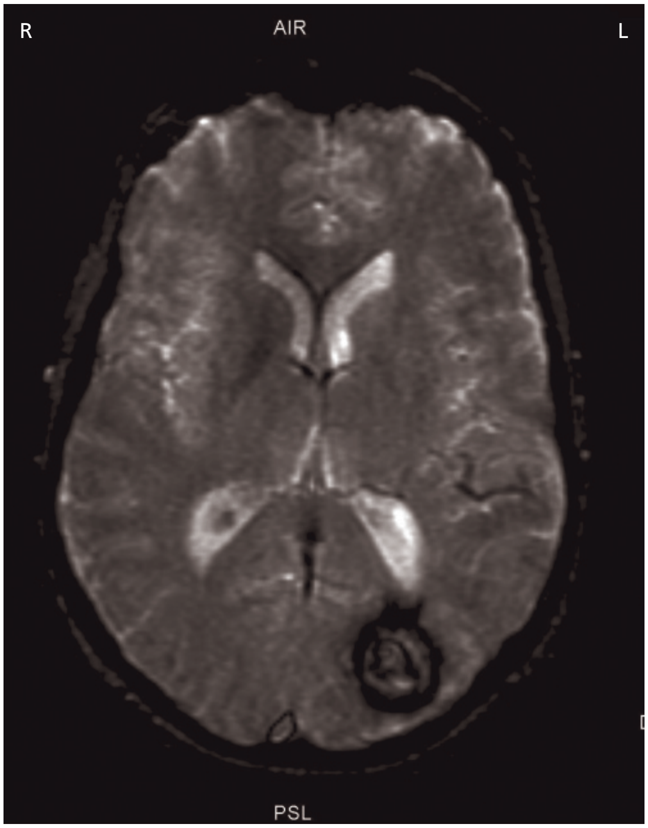

Figure 4.18 Occipital cavernoma (MRI T2*).

Dural fistulae

Dural arteriovenous fistulae (DAVF) are rare and can be found from adolescence to old age. They are most common in young adult women. They consist of an arteriovenous fistula with multiple arteries converging on a single venous structure. They are primarily fed by dural arteries but high-flow lesions can recruit pial branches. Different patterns of venous drainage are seen, e.g. drainage into a sinus with or without flow restriction or drainage into cortical veins either directly or by reflux from a venous sinus.

DAVFs are thought to be acquired lesions probably a result of venous thrombosis, usually silent, with development of collaterals. They may be located anywhere within the intracranial dura, although most are found adjacent to major dural venous sinuses, particularly the transverse sinus. Symptoms and signs differ greatly but are in the main caused by the pattern of venous drainage. Significant symptoms include haemorrhage, neurological deficit and intracranial hypertension. The overall risk of haemorrhage is approximately 2% per year; much depends on site and haemodynamics of the lesion. Rather than bleeding, common features are audible bruits, cranial nerve palsies and ocular signs such as papilloedema.

Head CT rarely detects a DAVF, although dilated veins may suggest its presence. MRI may demonstrate dilated feeding vessels and veins but is neither sensitive nor specific. Six vessel angiography, i.e. including the external carotid arteries, is necessary to detect and delineate a fistula accurately and is the optimal investigation.

Treatment of DAVFs has evolved over the last three decades. Cortical venous drainage is a risk factor for haemorrhage. Action is required in these cases. Patients without cortical venous drainage and without threat of visual loss from papilloedema have a benign natural history and may require no therapy. Treatment of these patients is justified only if the risk of complication is low. Sometimes palliation is necessary. The primary treatment has been surgical disconnection of the fistula and resection of the dural segment and venous sinus. Not surprisingly, this carries a high risk of substantial blood loss and morbidity. Recently, there has been less emphasis on resection of the venous sinus. This has proved as effective as sinus resection and the risk of venous infarction is lower. Therapeutic embolization can be used for either palliation or attempted cure. This can be achieved via transarterial and/and transvenous routes. DAVFs can also be treated with stereotactic radiosurgery with or without endovascular embolization of accessible feeding vessels. Partial prior endovascular treatment aims to reduce the risk of haemorrhage prior to the later obliteration of the DAVF by stereotactic radiosurgery.

Investigation of stroke and TIAs

Stroke investigation is aimed at identifying risk factors and confirming or refuting the clinical diagnosis. Investigation nearly always improves the clinician's understanding of the pathophysiology of the stroke or transient ischaemic syndrome. This then guides acute treatment and secondary preventative measures. It is facile to separate completed stroke from TIAs when considering appropriate investigation. The aetiologic spectrum is identical, although management may be very different.

Basic investigations for all

Simple tests

In all patients, basic blood screening should include full blood count to look for anaemia, polycythaemia, thrombocythaemia and thrombocytopenia. Anaemia of chronic disease may be a marker for endocarditis. Exceptionally, haematological malignancies may be complicated by stroke. Basic coagulation analysis should be undertaken in patients with haemorrhage and is especially important in those receiving anticoagulants or any other medication. Urea and electrolytes guide homeostatic management in the acute phase and may also reveal end-organ damage from hypertension. Patients with significant electrolyte disturbance may present with global or focal dysfunction. Plasma glucose is an essential triage test; diabetes is common and hypoglycaemia can cause focal signs. Hyperglycaemia is also associated with severe stroke. Rarely, hyperosmolar non-ketotic diabetic coma presents as a stroke. Basic lipid analysis for cholesterol and fasting triglycerides should be performed in all. Syphilis serology should be performed if the patient has been at risk at any time. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are non-specific screening tests for inflammatory arterial disease and endocarditis. Blood cultures and repeated urine examinations should be carried out if there any question of endocarditis. Thyroid function tests should be performed in all patients especially those with atrial fibrillation. In all patients, chest X-ray and electrocardiography (ECG) should also be carried out. The principal point of chest radiology is to establish the presence of a normal cardiac silhouette and look for consolidation. The ECG changes of note are left ventricular hypertrophy secondary to hypertension, previous or acute MI (possible cardiogenic embolus) and most importantly atrial fibrillation or other unsuspected dysrhythmia.

Imaging

Neuroimaging is essential. Although MRI is greatly superior to CT, it is not currently widely available as a routine acute investigation. Initial CT is performed to distinguish infarction from haemorrhage or reveal mimics of the stroke syndrome such as tumour or subdural haematoma. In the early stages depending partly on time interval, the size of infarction and the skill of the radiologist, CT may be negative. Only 50–70% of infarcts are ever visible with CT. It has become generally accepted that CT can diagnose a haemorrhage >0.5 cm accurately, i.e. exclude it, and indeed it is preferable to conventional MRI in the acute phase. However, patients with microhaemorrhage on gradient echo MRI may present with minimal impairments when CT and conventional MRI are normal. The very early CT changes of stroke are subtle, but the ability to read these is crucial in making decisions about the suitability of a patient for thrombolysis. The very early stages of cytotoxic oedema in the MCA territory are indicated by loss of the insular ribbon, and effacement of the sulci with obscuration of the lentiform nucleus, shown in Figure 4.19.

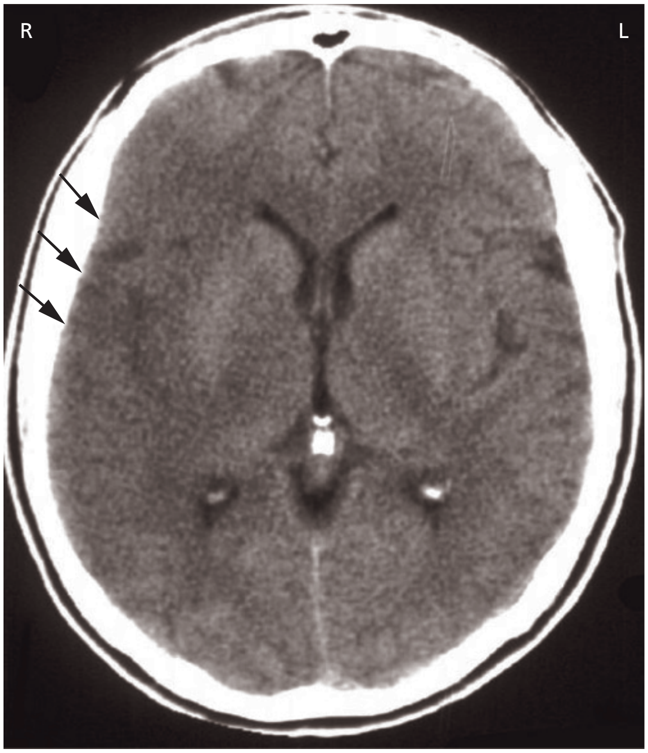

Figure 4.19 Early partial right hemisphere infarction following MCA occlusion. There is effacement of right temporal sulci, obliteration of the Sylvian fissure, with slight hypo-attenuation of the cortex, right temporal lobe and of the insula (unenhanced CT).

CT can indicate clearly large vessel occlusions (e.g. a dense outline of the MCA), pointing to a central cause for embolism, or multiple haematomas suggestive of amyloid angiopathy or vasculitis. The size of the infarct or haemorrhage will provide useful information relating to prognosis and the presence or likelihood of subsequent brain swelling. A small infarct in the territory of a lenticulo-striate penetrating vessel suggests a completed vascular syndrome, but if the anatomy suggested a more proximal MCA source then this would indicate the whole MCA territory is at risk. The role of CT in the diagnosis of SAH is discussed above.

MRI is a far more sensitive investigation than CT for both stroke and non-stroke pathology. It is especially superior in the posterior fossa and for revealing small areas of infarction secondary to penetrating vessel occlusion. Sophisticated multimodal imaging can also be used to distinguish acute from chronic infarction and may demonstrate microhaemorrhage. These techniques are likely to become critical to deliver safely hyperacute treatments such as thrombolysis. MRI has high sensitivity to detect cerebral venous thrombosis and can be used in conjunction with MR angiography to detect dissections of the carotid and vertebral arteries. The two most useful newer MR sequences are diffusion weighted imaging and susceptibility T2* sequences. Diffusion weighted imaging (DWI) maps the constant diffusion of water. This rapidly becomes abnormal after ischaemia returning a 'light bulb signal' indicative of restricted diffusion resulting from cytotoxic oedema. This usually indicates completed infarction but this is not absolute; some reversible diffusion changes have been demonstrated. Older infarcts may also appear bright on DWI ('T2 shine-through'), but these can be distinguished from acute infarcts by examining the Apparent Diffusion Coefficient (ADC) images that show acute infarcts as dark. DWI can be matched with clinical examination, MR perfusion imaging and MR angiography to ascertain whether there are salvageable areas of brain. In addition, DWI commonly refines the pathophysiological diagnosis of stroke, by separating into time intervals different areas of infarction and demonstrating acute multi-territory changes suggestive of cardiac embolus, not apparent on conventional MRI.

MR T2* sequences help demonstrate areas of microhaemorrhage not visible on conventional MR or CT. The distribution of these microhaemorrhages may point to amyloid (superficial location) or severe hypertensive arteriopathy (deep location). Patients with microhaemorrhage are at higher risk of primary intracerebral haemorrhage and have a more severe form of small vessel disease than those without haemorrhage.

In patients with haemorrhage in whom a non-hypertensive aetiology is suspected, it is necessary to exclude an AVM. In some this can be adequately achieved with MRI and/or MR angiography delayed until resolution of the haematoma. However, many such patients will require catheter angiography.

Conventional MR sequences are also useful in the diagnosis of cervical artery dissection (see below). MRI is sensitive and specific when used to image in cross-section the carotid artery from the bifurcation to the skull base. The vertebral artery is harder to image accurately and false positives are common and secondary to the vertebral venous plexus returning a 'dissection type' signal. MR angiography is also helpful here.

Whatever imaging modality is available, information derived should be used to build up the pathophysiological profile and to guide management. Most importantly, the imaging abnormalities must be concordant with the clinical picture. For example, the presence of acute or old infarction in non-symptomatic vascular territories should focus further investigation toward a central embolic source. Also, extensive asymptomatic small vessel disease is a risk factor for cerebral haemorrhage and help refine a decision away from anticoagulation in a patient in atrial fibrillation.

Imaging also has a critical role in managing patients with stroke who may benefit from neurosurgical intervention.

The recommendations published in 2004 by the UK Royal College of Physicians is that brain imaging should be undertaken as soon as possible in all patients within 24 hours of onset at the most, unless there are good clinical reasons for not doing so. It is likely that this guideline will be shortened to 3 hours given recent evidence that immediate scanning of suspected stroke is the most cost-effective strategy. Urgent (i.e. at 3 AM) imaging is recommended in a number of circumstances (Table 4.13).

Table 4.13 Recommendations for urgent imaging in stroke based on the Royal College of Physicians National Clinical Guidelines.

If thrombolysis or immediate anticoagulation is contemplated
If clinical deterioration or fluctuation occurs
If there is severe headache at onset or subarachnoid haemorrhage is suspected
If hydrocephalus secondary to intracerebral haemorrhage is suspected
If trauma is suspected
In patients on anticoagulants or with a known bleeding tendency
If the diagnosis is in doubt
If there is depressed consciousness, papilloedema, neck stiffness or fever
If there are unexplained progressive signs.

Many of these recommendations relate to the simple yet important principle that any patient with a depressed level of consciousness may need urgent neurosurgical intervention. One of the most important recommendations is that patients on anticoagulants should be imaged immediately.

Guided investigations following basic profile

Imaging, simple tests and the clinical profile should build up the pathophysiological diagnosis sufficiently to direct further investigation. Ischaemic stroke within the carotid territory should prompt the search for carotid stenosis. This is obviously essential in those in whom secondary preventative surgery would be considered. The emphasis is on non-invasive imaging, in preference to invasive techniques such as catheter angiography. Both MR angiography and duplex imaging are useful. If either is completely normal then the screen is adequate. If either suggests carotid stenosis greater than 50% or occlusion then it is very useful to carry out both tests. If they are concordant one can assume that the information is accurate. In patients in whom the information is non-concordant it may be necessary to perform contrast-enhanced MR angiography or formal catheter angiography. It should be appreciated that catheter angiography carries the risk of causing stroke, fatal or severely debilitating, especially in those with severe atherosclerosis, and it has other hazards (see below).

Ultrasound of the neck vessels in real time mode provides images in several arterial planes. It is accurate in experienced hands, at the carotid bifurcation, the major area of interest in most cases. It has a good sensitivity and specificity for occlusive lesions, but has limitations. Sometimes, the vertebral origin is difficult to image and small clots and ulcers are difficult to image at any site. Calcification may obscure the visualization of a stenosis. Arteries may be misidentified. For example, a carotid occlusion may be reported as trickle flow by mistaking a small cervical artery for the carotid. When real time mode is combined with Doppler the system is called duplex. The Doppler analyses flow patterns (average velocity of blood moving through a vessel) and the B mode the anatomy – the combination is better than either alone. Stenosis of an artery above a certain threshold increases peak systolic and diastolic blood flow velocity. Duplex is widely available and non-invasive but there are some difficulties. It is operator dependent and requires considerable experience. It is not completely sensitive or specific for high-grade stenosis.

Doppler can also be applied transcranially (TCD) and has significantly advanced the study of stroke. TCD can accurately detect atherosclerotic lesions in the intracranial ICA, MCA, intracranial vertebral artery the mid and proximal basilar. TCD may be used to detect emboli, acutely image intracranial vessel thrombosis and in some centres it has been used in combination with thrombolysis as a mechanical aid to clot dissolution. TCD may also be used to detect systemic right to left shunts, e.g. through a PFO. Agitated saline can be injected into a vein and the MCA insonated for arrival of small bubbles with a Valsalva manoeuvre.

Another safe sensitive non-invasive technique is MR angiography. MR angiography can accurately visualize the carotid bifurcation but may overestimate the degree of stenosis. MR angiography of the vertebral origin from the subclavian is disappointing in most cases, but the portions of the vertebral artery within the neck and within the intravertebral foramina are well shown. MR angiography (MRA) of the intracranial circulation is providing a useful screening tool both for aneurysms and occlusive disease.

The advent of MRA and duplex has led to a steady decrease in the indications for catheter angiography but this technique is still useful in selected circumstances. Intra-arterial angiography carries a small but definite risk of causing a stroke. The commonly quoted figure is 1% but inexperienced operators have a higher risk. The catheter or contrast can dissect the femoral artery and/ or cause 'trash foot' as a result of dislodging aortic or arterial atheroma. Contrast medium can occasionally precipitate renal failure and provoke allergic reactions. Some patients develop alarming, but usually temporary blindness after vertebral injections. The decision for angiography should be made carefully in a multi-disciplinary setting. The non-invasive tests must have been carried out first and usually a therapeutic decision must follow catheter angiography if this is to be performed. It is necessary to perform angiography in a number of vascular situations. In occlusive carotid disease, angiography may clarify discordant results from non-invasive tests, e.g. MRA suggests a 90% stenosis but duplex 50%. It may clarify sites not visible on non-invasive testing or subject to artefact (Figure 4.20). Catheter angiography is able to detect smaller aneurysms than MRA and is necessary following SAH when MRA is negative. It can be used to screen for underlying vascular malformations when MRI and MRA are normal and is often the only way of detecting dural fistulae. Despite the sophistication of MR venography, the venous phase of a catheter angiogram is superior and can clarify anatomic variants less clearly interpretable on MR. Currently, three-dimensional CT angiography is also improving and is likely to take over from catheter angiography in many cases.

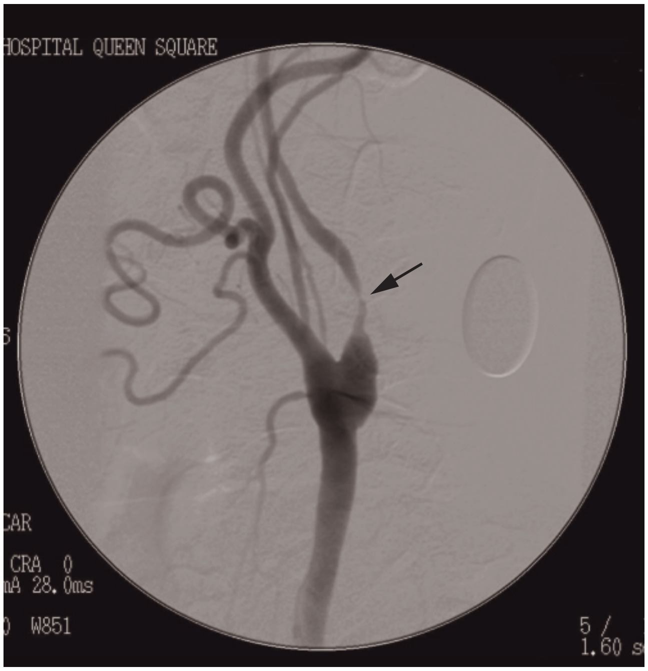

Figure 4.20 Severe left internal carotid artery stenosis (catheter angiogram).

The degree of carotid stenosis is defined currently by three different methods other than angiography. It is important to know which method is being discussed as the values differ; so does the evidence on which intervention is based. All three methods measure the diameter of the stenosis at the site of the maximal narrowing of the artery but the proportional stenosis that they produce is then calculated from different estimates of what the normal artery should have measured at that point, as the denominator. The European Carotid Surgery Trial (ECST) method used an estimate of the normal luminal diameter at the site of stenosis. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET) it is based on the distal carotid artery diameter. In the common carotid method, it is based on the common carotid diameter. These produce different measurements. The NASCET method produces a lower percentage stenosis than the ECST or common carotid methods for the same lesion at the carotid bifurcation.

Cardiac investigations

In patients with suspected cardiogenic embolus, transthoracic echocardiography can define wall motion abnormalities or the presence of atrial or ventricular thrombus. In selected patients with prosthetic valves, suspected aortic root disease and right to left shunts TOE provides better visualization than the transthoracic mode. If cardiogenic embolus is still strongly suspected despite normal chest X-ray, ECG and echocardiogram then sometimes Holter monitoring may be useful to reveal paroxysmal atrial fibrillation; monitoring may need to be prolonged. Echocardiography has a high yield in patients with known cardiac disease, with systemic embolic phenomena and when the stroke pathophysiology points to cardiac embolism (e.g. PCA occlusion). TOE is undoubtedly superior to transthoracic insonation, particularly as the left atrium is directly anterior to the oesophagus. TOE also visualizes the proximal aorta, e.g. for atherosclerosis. If previous blood cultures have been negative, consider repeating them.

Special investigations

Thrombophilia assessment is rarely useful in arterial stroke with the exception of antiphospholipid antibodies. It should be noted that antiphospholipid antibodies can be associated with many sorts of vasculopathy and they are not uncommonly seen coincidentally in patients with atherosclerosis. Venous thrombophilia may be relevant in the rare circumstance of a positive family history of thrombosis associated with embolic stroke through a PFO. Autoantibodies may mark a systemic vasculitis. In appropriate circumstances, screening for common mitochondrial and NOTCH III (CADASIL) mutations, leucocyte galactosidase A for Fabry's disease, homocysteine, syphilis and HIV serology should be carried out. Very occasionally, if an infective aetiology is suspected it will be necessary to examine the CSF. Drug screening should be carried out if drug abuse is suspected.

Management of acute stroke

Over the last two decades, stroke has changed from being seen as untreatable, to a condition where there is now a range of options for acute interventions, shown conclusively to improve outcome. In the first few hours after stroke, measures are designed to restore blood flow (reperfusion), preserve the ischaemic penumbra (neuroprotection) and prevent early recurrence (aspirin treatment). Admission to a stroke unit and multidisciplinary rehabilitation are vitally important and are complementary to medical treatments. It is now well-recognized that rehabilitation should start as soon as possible after onset of stroke (Chapter 17), aiming to optimize recovery, enhance neural plasticity and facilitate functional adaptation to any residual impairments as far as possible. Active rehabilitation consists of measures designed to facilitate and enhance recovery from impairments, such as physiotherapy training and measures to improve function, e.g. the provision of aids such as a walking cane, wheelchair or modified utensils. Part of successful rehabilitation requires the setting of goals. Successful stroke unit care also pays attention to the prevention of complications and the prevention of recurrent stroke, as described below.

An early accurate diagnosis of the underlying pathological cause and mechanism of stroke should have been made to guide appropriate therapy. In particular, it is essential to distinguish between haemorrhage and infarction by brain scanning. Ideally, a CT or MRI scan should be performed as soon as the patient is admitted to hospital. Most initial treatments are given without clear knowledge of the underlying pathology, apart from the distinction between haemorrhage and infarction, but it should be borne in mind that treatments such as thrombolysis, designed to lyse a clot, are unlikely to be effective if the cause of ischaemia is arterial occlusion by atheromatous debris or a dissecting haematoma. On the other hand, identification of the mechanism of stroke may lead to specific therapies, e.g. antibiotics for bacterial endocarditis, in addition to more generic treatments.

Organized care in a stroke unit

One of the most important aspects of stroke treatment is quite simple. It is to treat patients in an organized stroke unit. The trials of stroke unit care show that about 1 in 12 patients are saved from death or being dependent by being cared for on an organized stroke unit rather than in a general medical ward. The same benefits cannot be achieved by providing a mobile stroke team visiting general medical wards in hospital, nor by visiting patients in their own homes. More patients are discharged from stroke units to their own homes without increasing average length of stay. The benefits of stroke unit care appear to apply equally to elderly and young patients, to both genders and irrespective of whether the stroke is mild, moderate or severe. All patients should therefore be admitted to an acute stroke unit as soon as possible after onset, irrespective of age, gender or clinical severity, for multidisciplinary assessment and treatment. It is likely that all patients benefit from the provision of information, the positive attitudes to stroke and the organized provision of care on an organized stroke unit. From a public health perspective, the benefits of stroke unit care arising from the overall prevention of death, reduction in disability and need for institutional care are considerable when compared with individual pharmacological treatments. Also, organized stroke care is unlikely to harm anyone.

The reasons why organized stroke care benefits patients are complex. Factors identified that characterize stroke unit as opposed to general medical ward care (e.g. a discrete geographical area, multidisciplinary team meetings) are to some extent epiphenomena of a more fundamental difference. This simply is having an effective team that has ownership of the patient's problems and a responsibility to address them. The complex problems of patients with stroke go far beyond the strict medical issues and cannot be effectively addressed by a disjointed approach. It is likely that the benefits from organized care result first from better care of the acute patient (e.g. accurate diagnosis, appropriate use of drugs, prevention of swallowing complications/hypoxia/hypovolaemia, appropriate treatment of pyrexia, hyperglycaemia) leading to less secondary brain damage. Secondly, coordinated goal-orientated rehabilitation and discharge planning is a totally different proposition to more fragmented delivery of rehabilitation. Patients with intracerebral haematomas often gain considerably and as much from organized care as patients with ischaemic stroke. In contrast to ischaemic stroke, they take much longer to start to recover and need careful supportive care during this time.

The benefits of stroke unit care in the randomized trials were maximal when patients were admitted within a week of onset. The benefits are likely to be even greater where patients are admitted acutely for monitoring and provision of acute treatment such as thrombolysis. There are strong arguments for patients to be admitted to an acute stroke unit directly from the community or from the A&E department. Several models of service delivery of acute stroke care exist, depending on local circumstances. Some acute stroke units keep patients for 2–7 days before discharging those who require further therapy to a rehabilitation stroke unit. Other units combine acute and early rehabilitation care on one ward, keeping patients for up to 6 weeks before discharging them home or to alternative rehabilitation facilities. These facilities include community rehabilitation centres, community stroke teams providing treatment at home, rehabilitation facilities for care of the elderly and specialized neurological rehabilitation units.

Specific treatments for acute stroke

Thrombolysis

Thrombolysis is one of the most exciting, controversial and complex recent developments in stroke medicine. The first thrombolytic agent to be tried in acute ischaemic stroke in the 1980s was streptokinase, but this agent was found to cause an unacceptable incidence of cerebral haemorrhage and was abandoned. Later trials showed that alteplase, a recombinant tissue plasminogen activator, was far safer. The most convincing benefits of intravenous alteplase were shown in the National Institute of Neurological Disease and Stroke (NINDS) study, which randomized patients within 3 hours of onset of ischaemic stroke, half within 90 minutes of onset. The trial required a CT before treatment, and blood pressure was carefully controlled in those with raised readings, using intravenous drugs if necessary. One in 8 patients treated benefited in terms of making a full, or nearly full, recovery and the proportion of patients achieving a Rankin Grade 0 or 1 score at 3 months follow-up was 39% after alteplase treatment, compared to 26% after placebo. This benefit was accompanied by a significant risk of symptomatic intracranial haemorrhage after alteplase of 6%, compared to 1% in the placebo group. There was no significant difference in mortality rates between the two groups.

Subsequent trials of alteplase randomized patients up to 6 hours after onset of ischaemic stroke, but failed to show the striking benefits of the NINDS 3 hour study. Subsequent meta-analysis, combining the results of all previous major trials of intravenous thrombolysis with alteplase, has shown that there is a linear relationship between the time to treatment and the chances of benefit: the earlier patients are treated the better. These results led to alteplase receiving a licence for use in North America, Europe and elsewhere. The European Union licence has strict conditions, including limiting use to 3 hours from onset of stroke and insists that only experienced teams with neurological training should administer the drug. Beyond 3 hours from onset, the benefit remains uncertain. Further randomized trials are in progress to see whether the time window can be extended beyond 3 hours and to determine whether there are subgroups who benefit more or less from treatment within 3 hours.

Intravenous thrombolysis should only be offered to patients according to established protocols if they satisfy the inclusion criteria (Table 4.14). Patients treated with thrombolysis outside

Table 4.14 Guidelines for intravenous alteplase in acute ischaemic stroke.

Eligibility
Age 18 years or older
Clinical diagnosis of acute ischaemic stroke
Assessed by experienced team
Measurable neurological deficit
Glasgow Coma Score >8
Timing of symptom onset well established
CT or MRI and blood tests results available
CT or MRI consistent with diagnosis
Time since onset <3 hours at start of infusion

Exclusion criteria
Symptoms only minor or rapidly improving
Haemorrhage on pre-treatment CT (or MRI)
Suspected subarachnoid haemorrhage
Active bleeding from any site
Recent gastro-intestinal or urinary tract haemorrhage within 21 days
Platelet count less than 100×10^9/L
Recent treatment with heparin and APTT above normal
Recent treatment with warfarin and INR elevated
Recent major surgery or trauma within the previous 14 days
Recent post-myocardial infarction pericarditis
Neurosurgery, serious head trauma or previous stroke within 3 months
History of intracranial haemorrhage (ever)
Known arteriovenous malformation or aneurysm
Recent arterial puncture at non-compressible site
Recent lumbar puncture
Blood pressure consistently above 185/110 mmHg
Abnormal blood glucose (<3 or >20 mmol/L)
Suspected or known pregnancy
Active pancreatitis
Epileptic seizure at stroke onset

Cautions and limitations
Age >80 years
Severe neurological deficit (NIHSS >22)
Visible changes on pre-treatment CT of infarction > one-third of MCA territory
Diabetic retinopathy

APTT, activated partial thromboplastin time; CT, computerized tomography; INR, international normalized ratio; MCA, middle cerebral artery; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale.

the strict protocol have an unacceptable rate of complications, especially intracranial haemorrhage. Training and experience are required to diagnose stroke, exclude stroke mimics and interpret CT appearances in acute ischaemic stroke. Established infarction shows on the CT as a well-defined area of low attenuation. However, the early changes of infarction are often subtle. In MCA territory infarction, these include loss of distinction of the internal capsule and insular ribbon cortex, loss of cortical definition between grey and white matter, and effacement of the sulci (Figure 4.19). Although not part of the NINDS protocol, most experts would exclude patients with early signs of infarction involving a large proportion of the MCA territory, because such signs imply that ischaemia has already progressed to irreversible infarction. Patients and relatives need to accept that although thrombolysis provides a chance of some real benefit, there is also a risk of harm from cerebral haemorrhage. Patients should not be denied thrombolysis if consent cannot be obtained, e.g. because of aphasia. It is essential that the timing of symptom onset should be well established, so that patients are only treated within the guidelines, currently within 3 hours of onset. For example, patients who wake from sleep with deficit from an ischaemic stroke are not eligible for thrombolysis with alteplase.

Only a proportion of patients will be suitable for thrombolysis, especially because many patients will not reach hospital within 3 hours of onset. Nevertheless, changes in service delivery are required to institute thrombolysis, e.g. development of acute stroke teams and protocols to ensure that patients are scanned with alacrity. The proportion of patients reaching hospital in a timely fashion can be increased by joint hospital and ambulance service protocols, involving training of ambulance personnel in the recognition of stroke, so that patients with suspected stroke are taken directly to an acute stroke centre. Education of the public to recognize stroke symptoms and to summon emergency ambulance services immediately is also required.

In the future, selection of patients with persisting penumbra may play a part in selecting cases for thrombolysis. For example, a mismatch between a small area of infarction shown on DWI and of impaired cerebral blood flow shown on perfusion MRI may be an indication of salvageable penumbra, and this could allow the extension of the window for thrombolysis beyond 3 hours in patients who arrive late and have persistent mismatch. Alternative thrombolytic agents may also allow the time window to be prolonged. For example, desmoteplase shows promise as an intravenous thrombolytic agent when administered within 3–9 hours of ischaemic onset in patients with MRI perfusion–diffusion mismatch, but the agent needs to be tested in larger randomized trials. CT perfusion imaging is an alternative to perfusion MRI that may become more widely applicable in the future.

Another experimental approach to improving the effectiveness of thrombolysis is to combine intravenous alteplase with therapeutic transcranial ultrasound applied to the skull and focused on the site of arterial occlusion. Experimental studies have shown that ultrasound improves the activity of clot lysis, presumably by facilitating access of the thrombolytic drug to the core of the thrombus. Clinical trials have suggested an improvement in recanalization rates with continuous transcranial Doppler ultrasound given for a 2-hour period after administration of intravenous alteplase. Again, larger trials are required to demonstrate the benefit of this approach.

The majority of evidence in favour of thrombolysis relates to the intravenous route of administration. This reflects the ease and rapidity with which an intravenous transfusion can be administered. On the other hand, local arterial infusion of thrombolytic agents has the advantage that a preliminary angiogram can be performed to confirm arterial occlusion, and that the agent can be infused exactly where it is needed. Case series and the PROACT II randomized trial suggest that intra-arterial thrombolysis can be highly effective, even up to 6 hours after onset in selected patients. However, intra-arterial thrombolysis requires specialized facilities and experienced neuroradiologists, limiting its widespread applicability. Moreover, the need to establish arterial access increases the delay to treatment compared with the intravenous route. There are therefore studies in progress investigating the benefits of arterial thrombolysis following an initial intravenous dose of alteplase, to determine if this combination results in superior outcomes in patients who do not initially benefit from an intravenous agent. Intra-arterial thrombolysis may also have a particular role in patients with basilar artery thrombosis, possibly up to 12 hours after onset, particularly if infarction in the posterior circulation has not yet developed.

Mechanical recanalization

A number of devices are being developed to extract or break up thrombus occluding the larger intracranial blood vessels following acute ischaemic stroke, using microcatheters inserted via an endovascular approach. The use of mechanical devices will require specialized facilities and experienced operators, but in appropriate centres, the technique may provide an alternative to thrombolysis or an additional therapy for patients in whom thrombolysis has failed to achieve effective reperfusion.

Antiplatelet therapy in acute stroke

Two very large randomized trials have shown that aspirin, given within 48 hours of onset, has a small but significant benefit in reducing the rate of recurrent ischaemic stroke. About 1/100 patients treated with aspirin avoid death or disability without a significant increase in the risk of symptomatic cerebral haemorrhage. Although this benefit seems small, it translates into a substantial cost effectiveness, given the commonness of stroke and the low cost of aspirin. For example, in the UK it is estimated that if everyone with stroke were given aspirin within 48 hours of onset, preferably after a CT scan to exclude cerebral haemorrhage, then more than 1000 patients would be saved from death or disability every year. Aspirin has not been extensively studied in patients with cerebral haemorrhage, but the majority of experts and emergency physicians consider aspirin contraindicated in any cerebral haemorrhage or if there is substantial haemorrhagic transformation within an ischaemic stroke.

Currently, there are no randomized trials of antiplatelet agents other than aspirin, to establish their safety within the first week or so after the onset of stroke. Aspirin therefore remains the agent of choice in acute ischaemic stroke. We recommend a loading dose of aspirin 300 mg, followed by 75 mg daily. We would only use an alternative antiplatelet agent within the first week after onset in patients allergic or intolerant of aspirin. Antiplatelet therapy for longer term prevention is discussed below.

Anticoagulation in thrombo-embolic stroke

A large number of randomized trials have failed to demonstrate any overall benefit of early anticoagulation with standard heparin, or with low molecular weight heparins, either routinely in acute stroke or in patients with progressive stroke or acute cardioembolic stroke associated with atrial fibrillation. The latter is in contrast to the clear benefit of warfarin in the long-term prevention of stroke from atrial fibrillation. In the acute stroke trials, any reduction in the rate of recurrent ischaemic stroke related to anticoagulation was matched by an increased rate of symptomatic intracranial haemorrhage. The evidence shows that there is no place for the routine use of anticoagulation or subcutaneous heparin in acute stroke. However, given that the risk and benefits appear to be balanced overall, prophylactic low-dose subcutaneous heparin can be used in patients who are thought to be at high risk of deep vein thrombosis, e.g. immobile patients with a previous history of deep vein thrombosis. We recommend the routine use of anti-embolism stockings for all cases. Stockings are currently being tested in a randomized trial. Early mobilization, e.g. sitting the patient up the day after stroke, and active physiotherapy play an important part in limiting deep vein thrombosis.

There may also be a role for the use of intravenous heparin in selected patients who are thought to be at high risk of early stroke recurrence. We use heparin in patients with demonstrated thrombus in the heart, or those with acute vertebral or carotid artery occlusion, so long as the patient does not have a large infarct (more than one-third of MCA territory by volume). In these latter cases the risk of symptomatic haemorrhagic transformation may be increased. Anticoagulation is often recommended in patients with carotid and vertebral artery dissection (see below), so long as the dissection is limited to the extracranial portions of the artery, but the benefits and risks of this treatment have not yet been shown in randomized trials. In patients in whom there is a good indication for long-term anticoagulation, e.g. atrial fibrillation, we delay anticoagulation for 2 weeks if the infarct is large.

Neuroprotection

Many neuroprotective drugs, designed to block various components of the biochemical cascade leading to cell death after an ischaemic insult, have been shown to reduce the size of infarction in animal models of ischaemic stroke. To date, none of these agents has fulfilled their promise in randomized trials in human stroke. A number of factors may be responsible for this failure to translate animal research to the bedside, including inability in clinical trials to replicate experimental conditions and inclusion of patients too late – up to 24 hours after onset of stroke. In animal studies of neuroprotection, agents are usually only effective if given within an hour or two after induction of ischaemia. Nevertheless, a free-radical trapping agent, known at present as NXY-059, looks promising. This was tested after initiation within 6 hours of onset in acute ischaemic stroke patients in the SAINT-1 Study. The drug resulted in significantly improved Rankin scores at 90 days in about 1 in 20 patients treated. Patients who received thrombolysis with alteplase and NXY-059 also had a lower rate of symptomatic haemorrhagic transformation. However, other measures of outcome, including a neurological impairment score, did not improve. Benefits were not found in the larger SAINT-2 Study.

The only licensed drug with an apparent protective benefit is nimodipine, given after recent SAH. In the British Aneurysm Trial, nimodipine reduced the incidence of cerebral infarction and the proportion of patients with a poor outcome by about 10%. Nimodipine has been shown to have no effect, or even to be harmful, in patients with ischaemic stroke and it is therefore possible that the benefits in patients with SAH arose because the patients can be pre-treated before the onset of ischaemia from vasospasm, or because nimodipine reduces severity of vasospasm.

Maintenance of homeostasis

Although drug therapy to protect the brain against the effects of ischaemia may not be beneficial, it is still logical to maintain the brain's physiological and biochemical environment in normal homeostatic balance, to preserve the penumbra and take all steps to prevent secondary deterioration. However, there is no trial evidence that the measures we recommend below to maintain homeostasis improve final outcome. Oxygen saturation should be monitored routinely and hypoxaemia treated appropriately.

Blood sugar levels are elevated in about one-quarter of all stroke admissions. This includes patients with known and undiagnosed diabetes, and patients in whom elevation in blood glucose appears as a stress response. Mortality, poor outcome and infarct size are increased in patients with raised blood glucose, but whether the larger size of infarction contributes to the high blood glucose, or vice versa, is uncertain. Nevertheless, we recommend avoiding administering intravenous glucose in patients with acute stroke, and we institute insulin therapy on a graded scale when the blood glucose is >10 mmol/L, to maintain optimal levels within 6–9 mmol/L. Equally, hypoglycaemia should be avoided.

The majority of patients with acute stroke have raised blood pressure on admission, often because of pre-existing hypertension and an invariable hormonal or autonomic response to the stroke itself. The blood pressure readings usually fall over the course of the first week. It is not clear whether hypertension in the acute stage is harmful or even beneficial. Trials are therefore in progress, raising or lowering high blood pressure in acute stroke. Until the results of these trials are available, we recommend continuing any previously prescribed antihypertensive agents, but do not intervene to lower blood pressure unless the patient is a candidate for thrombolysis, has hypertensive encephalopathy, malignant hypertension or the blood pressure readings are above an arbitrary threshold of 200/120 mmHg. Over-vigorous lowering of blood pressure in acute stroke can certainly lead to extension of the infarct. In most cases, blood pressure should therefore be lowered using oral agents, although in patients in whom thrombolysis is appropriate, intravenous medication with labetalol is used. This should be given at a dose titrated against the blood pressure. The latter should be closely monitored in any patient receiving hypotensive therapy to avoid precipitous falls in blood pressure, aiming for systolic readings of 150–185 mmHg. Intramuscular agents should be avoided because of their unpredictable effect on blood pressure. In other cases, we would recommend that the institution of medication to treat hypertension should be delayed for 48 hours or more after onset.

Spontaneous hypotension after stroke is rare, but may occur if the patient develops cardiac problems or becomes dehydrated. Hypotension should be corrected promptly by raising the foot of the bed, fluid replacement and stopping hypotensive medication. Occasionally, inotropic medication may be required.

Pyrexia is associated with poor outcome of stroke, while animal studies show that even a small fall in body temperature is associated with smaller infarct volumes. Hence, we recommend that all patients should have fever treated vigorously, e.g. with paracetamol, and infections should be treated promptly with antibiotics. In clinical practice, therapeutic hypothermia is difficult to achieve, requires intensive care and is associated with significant complications on rewarming, and has therefore not entered routine clinical practice.

Treatment of cerebral oedema

Cerebral infarction is associated with failure of membrane pumps and influx of water into the cells. Cytotoxic oedema is therefore an inevitable consequence of cerebral infarction, and it is this feature that allows infarcts to be seen on CT. All infarcts are associated with a degree of swelling of the ischaemic tissue, which is manifest in larger infarcts on imaging by compression of the sulci and ventricles. The swelling of the infarct may last up to 4 weeks before the oedema resolves. In large hemispheric infarcts, this mass effect can cause transtentorial herniation with compression of the brainstem and is the most common cause of death in the first week after cerebral infarction. Typically, in patients with symptomatic cerebral oedema, the patient appears stable after the onset of symptoms for the first 24–48 hours, and then deteriorates on the second or third day, with progressive impairment of consciousness, coma and respiratory failure. This most often occurs in a patient with a large infarct caused by MCA occlusion, which is then sometimes known as malignant MCA infarction. Direct brainstem compression may also occur in patients with large cerebellar infarcts.

Cytotoxic cerebral oedema secondary to infarction tends to be unresponsive to steroids, but mannitol may provide a temporary respite pending surgical treatment. Paralysis and hyperventilation are rarely of benefit. Instead, decompressive neurosurgery with a large craniectomy should be considered, particularly in younger patients with non-dominant malignant MCA infarction, and in patients with brainstem progression secondary to cerebellar infarction. Craniectomy may be life-saving, and surprisingly good outcomes obtained in selected patients.

Patients with cerebral haemorrhage may also deteriorate because of oedema and transtentorial herniation, or direct brainstem compression. Occasionally, cerebral infarction, usually in the cerebellum, is associated with the development of hydrocephalus from compression of the aqueduct, although this is much more common following intracranial haemorrhage. Hydrocephalus may require shunting, or evacuation of the infarct or haemorrhage (see above).

Management of progressive stroke

About one-third of patients with ischaemic stroke progress in the first day after onset. Acute progression is even more common in patients with cerebral haemorrhage because of continued bleeding and enlargement of the haematoma. In ischaemic stroke, the causes of early progression are often unclear, but may include extension of the area of ischaemia from thrombus propagation, recurrent embolism, failure of initially adequate collaterals or enlargement of the penumbra from release of cytotoxic chemicals and the local effects of cytotoxic oedema. In patients who deteriorate after a period of stability, a number of causes need to be considered:

- Metabolic disturbances, e.g. low or high blood sugar, or hyponatraemia;
- Hypotension, or severe hypertension;
- Cardiac arrhythmias or myocardial infarction;
- Pyrexia and infections;
- Dehydration;
- Hypoxia, e.g. from aspiration, infection or silent pulmonary embolism;
- Cerebral oedema or hydrocephalus;
- Haemorrhagic transformation of infarction;
- Vasospasm after subarachnoid haemorrhage; and
- New infarction (often from cardiac embolism) or haemorrhage in a new location.

Patients who deteriorate should therefore be investigated for these possibilities by repeat CT or MRI, chest imaging and appropriate blood tests. Management will depend on the findings.

Common medical complications of stroke

Frank dysphagia, or an unsafe swallow with the risk of aspiration, is very common and occurs in about one-third of patients with hemispheric stroke and two-thirds of those with brainstem stroke. This can easily cause aspiration pneumonia, leading to hypoxia and stroke progression. All acute stroke patients should therefore have their swallowing assessed as soon as possible, using an agreed protocol. They should be kept nil-by-mouth until their swallowing has been assessed as safe. It is very likely that dehydration and starvation are harmful in the acute stages of stroke and fluid replacement should commence as soon as the patient is admitted if swallowing is not safe. It also makes sense to start feeding patients immediately. Even if a patient can swallow safely, the spontaneous intake of food and liquid is often inadequate because of poor appetite, cognitive impairment, neglect or physical difficulties in feeding. Nurses and carers should therefore have adequate time to help a patient to eat and drink sufficiently. When the oral route is not safe or practical, it is essential to establish other routes. In the short term, it is often convenient to replace fluids via an intravenous line, but this has the disadvantage of immobilizing the patient. A nasogastric tube is therefore preferred, with the advantage of allowing feeding as well as fluid replacement, with less risk of cardiac overload or line infection. If nasogastric tube feeding is likely to be required for more than 2 weeks, consideration should be given to inserting a percutaneous endoscopic gastrostomy (PEG) tube. This is usually preferred by patients and has the advantage that a large tube can be used. However, there are some risks of tube insertion, including peritonitis. Overall, there is little difference to the outcome after early PEG feeding compared with a nasogastric tube. It should be borne in mind that nasogastric tubes may increase the risk of gastrointestinal haemorrhage.

Deep vein thrombosis is usually seen in severely hemiparetic limbs and is very common on radiographic studies. Pulmonary embolus is a rare but important cause of death after stroke. The prevention of deep venous thrombosis is discussed above in the section on anticoagulation.

Pressure sores should be vanishingly rare and can be avoided by frequent turning of immobilized patients and the use of special bedding, e.g. air mattresses. Early mobilization and sitting the patient out of bed as soon as possible after onset also play a part in preventing pressure sores and other complications of immobility.

Shoulder pain is a common complication of stroke, largely preventable by good positioning of the shoulder and early physiotherapy. In particular, a paralysed upper limb should not be allowed to hang unsupported at the side of the patient, because the weight of the limb leads to subluxation of the shoulder joint and subsequently a painful frozen shoulder. The correct position of a patient in a bed or chair, with the weak limb supported at all times by a comfortable pillow or similar support, is essential. Patients who do experience shoulder pain may benefit from standard rheumatological treatments, including local steroid injections. The paralysed upper limb must never be neglected from motor therapy as it will contract and become dysfunctional and painful.

Limb swelling of the hand or foot of a hemiparetic limb is common and is partly explained by excessive sympathetic activity. The patient often complains that the limb is cold, because vasodilatation results in heat loss, even though the limb may feel warm to touch. This type of oedema should be distinguished from oedema secondary to a deep venous thrombosis. Elevation of the limb may help. Diuretics are not indicated.

Spasticity is a common but not universal feature of the upper motor neurone lesion resulting from infarction or haemorrhage. The increase in tone often develops several days or weeks after the onset of stroke. In the upper limb, the pattern of spasticity usually leads to flexion at each joint, and in the lower limb to extension. Early mobilization and appropriate physiotherapy probably play an important part in limiting the development of severe spasticity, and particularly the development of contractures. Oral drug treatment has a limited role in treating spasticity in stroke. The problem is that drug treatment often results in generalized muscle weakness and function is rarely improved. However, local injections of botulinum toxin into individual muscles may benefit patients in whom spasticity is causing focal problems.

Depression is very common after stroke and may reflect a direct neurophysiological cause, as well as reaction to the illness and persistent disability. Depression is associated with poor outcomes and should therefore be treated vigorously and expert psychiatric advice sought if necessary.

Post-stroke pain (Chapter 22) is characteristically associated with infarction in the thalamus and often develops weeks or even months after the onset of stroke. The pain is often described as a deep burning pain throughout one side of the body, which limits the patient's activities and may lead to severe depression. Standard analgesics are often ineffective, but relief may be obtained with tricyclic antidepressants, particularly amitriptyline taken at night, or anticonvulsants, e.g. gabapentin. Occasionally, transcutaneous nerve stimulation is helpful.

Dystonia is a rare complication of stroke involving the basal ganglia and usually develops some months after the initial event. Chorea appears to be particularly common in patients with the Moyamoya syndrome (see below).

Secondary prevention

Secondary prevention implies specific evidence-based measures that improve the prognosis following a defined clinical event. In the case of TIA, this implies preventing, to some degree, the risk of subsequent stroke. Following a stroke, secondary prevention means recommending and/or adopting measures that have been shown to prevent a further stroke. Advice that is not based upon evidence, nor widely agreed, is frequently given to patients in these clinical settings. Much of the evidence related to primary prevention, such as the control of hypertension, also applies to secondary prevention.

Secondary prevention after TIA and stroke

Patients who have had a TIA are at high risk of stroke and those who have had a stroke are at high risk of recurrent stroke. Both are at risk of MI. As a general figure, following either of these events, the risks of stroke or a recurrent stroke are about 5% per annum, but can be as high as 30% in patients with severe carotid stenosis. In general, the older the patient, and the more risk factors present, the greater the risk of recurrence. There is therefore much to be saved by effective measures to prevent recurrence. Treatment should be based on addressing risk factors and the results of investigations, together with an assessment of the degree of risk and benefits of treatment in individual patients. Targets for preventive measures include the following:

- Lifestyle risk factors;
- Lowering blood pressure;
- Lowering cholesterol by statin therapy and diet;
- Optimizing treatment of other conditions that promote vascular disease, e.g. diabetes;
- Prevention of cardiac embolism, e.g. valve surgery or anticoagulation;
- Targeted treatment for atherosclerotic stenosis by endarterectomy or stenting; and
- Inhibition of platelet aggregation with antiplatelet agents.

In patients with a history of cerebral haemorrhage, prevention should be targeted only at the first four issues and, in general, antiplatelet therapy and anticoagulation are contraindicated. Sources of cerebral haemorrhage, particularly aneurysms and AVMs may require specific treatment as previously described.

Following thrombo-embolism, treatment to prevent recurrence should start immediately after a TIA or recovery from a minor stroke, and in patients with more severe stroke, specific measures to prevent recurrence should be routinely considered and therapy started at around 2 weeks after onset. In patients who are very disabled, some preventive measures may need to be delayed, e.g. carotid endarterectomy, until the patient has recovered sufficiently. Anticoagulants and antiplatelet therapy have a rapid effect at reducing risk in appropriate patients. However, lowering of blood pressure appears to take several months to be effective at reducing risk, and the maximum benefits are not achieved for up to 2 years. Lowering cholesterol by statins also appears to take a year for benefit to be evident.

There is much to be gained by effective secondary prevention of stroke. The patient who stops smoking will halve their risk of stroke, a patient with atrial fibrillation taking warfarin will reduce their risk of stroke by two-thirds, and a patient taking simvastatin 40 mg/day and a combination of aspirin with an extended release form of dipyridamole will have their stroke risk reduced by 30% for each of these measures. Carotid endarterectomy in patients with recent symptoms and severe carotid stenosis may reduce the risk of recurrence by as much as 80%. Each of these treatment modalities acts independently. Thus, patients with multiple risk factors stand to benefit considerably from multiple manoevres.

Lifestyle modification

Patients with the relevant risk factors should be strongly advised to stop smoking, eat healthily to reach and maintain a normal weight, to take regular exercise and to reduce excessive alcohol consumption.

Lowering blood pressure

Epidemiological studies have established clearly that the lower an individual's blood pressure, the lower the risk of stroke, even within the normal range. In patients with hypertension, it is therefore likely that the lower the blood pressure is reduced with treatment the better, so long as the patient does not develop unwanted effects. Thus, we suggest that if the patient is at any risk of recurrence and can tolerate the medication, the British Hypertension Society (BHS) guidelines (optimum targets: below 140/85 mmHg in general and below 140/80 mmHg for patients with diabetes) should be followed closely, i.e. the blood pressure maintained at levels lower than these. This may require the use of three or four antihypertensive agents. At one time, there was concern that lowering the blood pressure in patients with prior stroke might be harmful, but the PROGRESS trial established that even patients with a relatively normal blood pressure after a stroke (often achieved with prior medication), benefited from further reduction in their blood pressure using a combination of an angiotensin converting enzyme (ACE) inhibitor and a diuretic.

Most experts believe that the benefits of lowering blood pressure in preventing stroke are related to the degree in reduction of blood pressure, not the drug class used to lower it. However, there is some evidence that β-blockers are less effective than other classes of antihypertensive agent. The authors usually start treatment with a thiazide diuretic and then add an ACE inhibitor, e.g. perindopril or ramipril. If further reduction in blood pressure is required, calcium antagonists can be added. The target of treatment should be to lower the blood pressure as low as tolerated, and certainly to ensure readings below the British Hypertension Society guideline figures.

Diabetes mellitus

Both Type I and Type II diabetes are well-recognized risk factors for stroke, probably because of the association of atherosclerosis and hypertension with diabetes. In keeping with this assumption, vigorous control of hypertension has more benefit in reducing the incidence of stroke in patients with diabetes than tight control of blood sugar levels. However, it is important to maintain HbAc1 levels at less than 7% if this feasible.

Lowering cholesterol

There is now convincing evidence from the Heart Protection Studies and the SPARCL study that lowering cholesterol with a statin after ischaemic stroke dramatically reduces the risk of recurrent stroke and MI. The lower the achieved level of cholesterol the lower the risk, with an approximately 25% reduction in the risk of recurrent ischaemic stroke and MI associated with a reduction in LDL cholesterol of 1.0 mmol/L. The benefits of statin therapy are therefore greater than those of antiplatelet therapy. All patients with stroke and TIA should therefore be considered for statin therapy, unless they have a cholesterol of <3.5 mmol/L or unlikely to have atherosclerosis (e.g. patients under the age of 40).

Anticoagulation

Anticoagulation in acute stroke has been discussed above. In contrast to the lack of benefit of heparins in acute stroke, there is good evidence that anticoagulation with warfarin prevents recurrent stroke in patients with cardio-embolic sources of thrombus (Table 4.15). The evidence is best for atrial fibrillation (AF), which is associated with a very high rate of recurrent stroke. In the European Atrial Fibrillation Trial, warfarin reduced the rate of recurrent TIA and stroke from 12% per annum down to 4% per annum, a two-thirds reduction in risk. In contrast, aspirin was much less effective, reducing the rate of recurrence by only about one-sixth. It is likely that warfarin works more effectively than aspirin because it affects the formation of thrombin-based clots in the heart, whereas antiplatelet agents are more effective at preventing thrombus starting with platelet aggregation on atheromatous clots. Thus, warfarin is the treatment of choice in patients with AF following stroke or TIA to prevent recurrence. In the elderly, the risks of intrcranial haemorrhage (including subdural haematoma), the need for regular monitoring and the issue of compliance, especially if there is cognitive impairment, need to be considered. In patients with contraindications to warfarin therapy, aspirin should be prescribed, bearing in mind that it is likely to be much less effective. Other antiplatelet agents have not yet been shown to be more effective than aspirin in patients with atrial fibrillation, but should be used in patients unable to take warfarin or aspirin. Fixed or low dose warfarin therapy is not effective in preventing embolism in patients with atrial fibrillation. In the future, it is possible that fixed doses of an oral direct thrombin inhibitor will provide a more convenient alternative to warfarin therapy, depending on the results of current randomized trials.

Table 4.15 Indications for anticoagulation in secondary stroke prevention.

Established indications

Cardiac embolism
- Atrial fibrillation
- Mechanical valve prosthesis
- Recent myocardial infarction
- Left ventricular aneurysm
- Dilated cardiomyopathy

Cerebral venous and venous sinus thrombosis

Possible indications

Recent major vessel occlusion
- Internal carotid artery occlusion
- Basilar artery occlusion

Recent extracranial cervical arterial dissection
Severe carotid stenosis prior to surgery or stenting
Crescendo TIAs despite antiplatelet therapy
Thrombophilia and prothrombotic states
Paradoxical embolism

Anticoagulation is indicated as a life-long treatment for patients who have had heart valves replaced with mechanical prostheses. If such patients have a cerebral haemorrhage while on warfarin, the treatment can be relatively safely stopped empirically, but should be restarted after 2 weeks. Other cardiac conditions associated with a high likelihood of the development of cardiac embolism listed in Table 4.15 should be considered for anticoagulation.

Possible indications for anticoagulation after stroke are also listed in the Table 4.15. Evidence that anticoagulation is superior to aspirin in all these disorders is lacking. It needs to be borne in mind that there are significant long-term risks of warfarin therapy, including a risk of 1–2% of intracranial haemorrhage per annum. We therefore usually only recommend anticoagulation for short periods in patients with uncertain indications to cover the period of time when their risk of recurrence is highest, e.g. for a maximum of 6 months after an acute ischaemic event.

The usual target International Normalized Ratio (INR) for the treatment of atrial fibrillation is 2.5 (range 2.0–3.0). For patients with mechanical prosthetic valves, a higher INR target to 3.5 (range 3.0–4.0) is usually chosen. A target INR of 2.5 is appropriate for most other indications. Analysis of the Atrial Fibrillation Trials suggests that an INR of 2.0 or less is insufficient to prevent thrombo-embolism, while the risk of haemorrhage rises substantially with an INR of above 4.0. It is important that anticoagulant clinics, and the patients themselves, are aware of these recommended levels.

The management of patients who are found to have a PFO, in association with TIA or stroke, remains controversial. There appears to be an association between PFO and cryptogenic stroke, i.e. those patients in whom no other cause is evident after full investigations. However, whether the mechanism of stroke in these patients is paradoxical embolism from cryptic deep vein thrombosis, embolism of thrombus formed in the PFO itself, or some unrelated mechanism, is not clear. Nevertheless, careful observational studies have suggested that the rate of recurrent stroke in patients with PFO treated with aspirin alone is as low, as the rate in patients with cryptogenic stroke without PFO, except if the PFO is associated with atrial septal aneurysm, when the risk may be increased. There appears to be little consistent relationship between the risk of stroke treated with aspirin and the size of the PFO. In patients where the PFO is thought to be relevant to the mechanism of their stroke, the PFO can be closed using percutaneous techniques and mechanical devices. The risks of this treatment are low, but not zero, and the long-term consequences of having a prosthesis in the heart are uncertain. We therefore favour treatment with aspirin in the majority of cases. The evidence suggests that warfarin is no more effective than aspirin in these patients.

For non-cardioembolic stroke, a number of randomized trials have shown that warfarin is no more effective than aspirin in preventing recurrent stroke in patients who have had TIA or stroke that has not been attributed to atrial fibrillation or a cardiogenic source, i.e. patients with stroke attributable to atherosclerosis, small vessel disease or cryptogenic mechanisms. Antiplatelet therapy is therefore preferred to anticoagulation in patients with this type of stroke, sometimes known as atherothrombotic stroke. The danger of warfarin therapy in this group of patients was emphasized by the results of the Stroke Prevention in Reversible Ischaemia Trial (SPIRIT), which was stopped prematurely because of an excess of brain haemorrhage in patients randomized to warfarin, compared with those randomized to aspirin after a recent TIA or stroke – in patients who did not have atrial fibrillation or cardiac embolism. Most of the haemorrhages occurred in patients over the age of 75 and in those who had moderate or severe small vessel disease (leuco-araiosis) on CT. This trial used a high target range for INR of 3.0–4.0, which may have increased the risk of cerebral haemorrhage; nevertheless, extensive leuco-araiosis should be considered a relative contraindication to warfarin therapy.

There is no evidence that patients with recurrent stroke or TIA symptoms on antiplatelet therapy benefit from anticoagulation, but we do regard recurrent symptoms as an indication to repeat or extend investigations, e.g. TOE, and prolonged Holter to exclude a cardiac source of embolism. In patients who have recurrent symptoms on warfarin, it is also important to review the diagnosis, and if the symptoms are likely to be the result of cardiac embolism, and the INR is in the target range at the time the patient has recurrent symptoms, consideration can be given to adding an antiplatelet agent, e.g. low dose aspirin 75 mg/day. However, the evidence suggests that the combination of aspirin and warfarin significantly increases the risk of gastrointestinal haemorrhage, and we are cautious about prescribing the combination.

Antiplatelet therapy

Aspirin has been the mainstay of treatment to prevent recurrent stroke for many years in patients who are not anticoagulated, and has the advantage of being very cheap. However, it should be borne in mind that antiplatelet therapy has less relative benefit in reducing the risk of vascular events than lowering blood pressure or lowering cholesterol. In a meta-analysis looking at the overall benefit of aspirin after stroke or TIA, the overall relative risk reduction in the combined outcome of stroke, MI or vascular death in different trials was only 13%. Aspirin also has the disadvantage of frequent side effects, particularly at high doses, including gastrointestinal haemorrhage and intracranial haemorrhage, which have incidences of approximately 27 and 5 per 1000 patients per year, respectively. The most common side effect is gastrointestinal irritation, and as many as 25% of patients discontinue aspirin treatment within a year or so of starting. Gastrointestinal side effects are less troublesome at lower doses. There is little evidence for a significant difference in effectiveness at any dose above 30 mg/day, and we therefore recommend using the lowest easily available convenient dose, which in the UK is 75 mg once daily.

There has been considerable interest in developing alternative, more effective antiplatelet agents than aspirin. The first widely used alternative to aspirin was dipyridamole. Initially, there was doubt about the effectiveness of dipyridamole in preventing stroke, but the Second European Stroke Cooperative Study (ESCS-2) showed that dipyridamole in a modified released preparation at a dosage of 400 mg/day had a similar effectiveness to aspirin in preventing recurrent stroke in patients with recent stroke or TIA. The combination of low dose aspirin and dipyridamole was significantly superior to aspirin or dipyridamole alone, with a relative reduction in stroke recurrence, compared with placebo, of 37%. These results have recently been confirmed by the ESPRIT trial. Dipyridamole is a very safe antiplatelet agent, and does not appear to significantly increase the risk of bleeding, even when combined with aspirin. However, it is not well tolerated by a significant proportion of patients because of side effects, particularly headache. These side effects may be minimized by starting with a low dose of dipyridamole and increasing the dose gradually, and may work in some patients over a few weeks, if they persist in taking the tablets. In ESCS-2, nearly 30% of patients discontinued combination therapy because of side effects.

The National Institute of Clinical Excellence (NICE) in England, in its 2004 appraisal of antiplatelet agents for the prevention of thrombosis in patients with stroke, recommended that all patients with recent stroke and TIA should be started on the combination of aspirin and dipyridamole, and that the medication should be continued for 2 years. Thereafter, NICE recommended that patients should be treated with aspirin alone.

Clopidogrel is an antiplatelet agent that was developed as a replacement for ticlopidine, an older antiplatelet agent that had the disadvantage of a 1% incidence of neutropenia. Clopidogrel 75 mg/day was compared with aspirin in the CAPRIE trial, and was shown to be slightly better than aspirin in the prevention of the combined outcome of all vascular events in patients with recent stroke, MI or peripheral vascular disease. However, the absolute reduction in vascular events attributed to clopidogrel over and above the benefit of aspirin alone was only 0.5%, i.e. the number needed to prevent one additional event was 200 patients over 2 years. Clopidogrel is considerably more expensive than aspirin, and slightly more expensive than dipyridamole. Moreover, CAPRIE was not powered to demonstrate effectiveness in the subgroup of patients randomized after stroke. Hence, NICE concluded that it was not cost effective as a first line treatment for stroke and TIA patients. Nevertheless, clopidogrel provides a good alternative for patients unable to tolerate aspirin or dipyridamole. NICE recommended that patients who are hypersensitive or unable to tolerate aspirin should be treated with clopidogrel. Although widely used as a substitute for aspirin in patients with recurrent symptoms while taking aspirin, or aspirin and dipyridamole (often known as aspirin failures), there is no evidence that this approach is effective. Clopidogrel is slightly better tolerated than aspirin in terms of gastrointestinal symptoms, but has a slightly higher rate of rash and diarrhoea as side effects. The rate of haemorrhage associated with clopidogrel is similar to that of aspirin.

The combination of clopidogrel and aspirin is no more effective than either drug alone in preventing recurrent stroke. In the MATCH trial, clopidogrel plus aspirin was compared with clopidogrel alone in patients with recent stroke considered at a high risk of recurrence. In this trial, there was a significant increase in the risk of cerebral haemorrhage in patients treated with the combination, without any significant reduction in the rate of ischaemic stroke. Thus, the combination of aspirin and clopidogrel cannot be recommended for the prevention of stroke, except in specific situations, e.g. in patients being treated following carotid stenting.

Management of carotid stenosis

Symptomatic carotid stenosis

The large randomized trials comparing carotid endarterectomy with medical treatment alone have demonstrated that patients with recent ipsilateral TIA or stroke, who are fit for surgery and have significant carotid stenosis, benefit from carotid endarterectomy to remove the stenosis (Table 4.16). The benefit of surgery is strongly related to the severity of the stenosis and the recentness of symptoms. The risk of recurrent stroke in patients with recent TIA who do not have carotid endarterectomy and are treated medically increases substantially above 50% stenosis with increasing deciles of stenosis over the next 5 years. Carotid endarterectomy has a risk of causing a stroke or death at the time of the surgery, in good hands, of about 6% in recently symptomatic patients, but thereafter removing the stenosis surgically almost abolishes the risk of ipsilateral recurrence, with a subsequent annual rate of stroke of only about 1%. The risks of surgery bear little relationship to the severity of internal carotid artery stenosis. Hence, the benefits of surgery increase with increasing degrees of stenosis above 50% or so, in patients with recently symptomatic stenosis (Figure 4.21). However, patients with very severe stenosis in which the distal internal carotid artery has collapsed (an appearance referred to as pseudo-occlusion or near occlusion on angiography) have a low risk of recurrent stroke and do not benefit from surgery. Patients with complete carotid occlusion were not included in the endarterectomy trials, but previous studies suggested that surgery for carotid occlusion was hazardous.

Table 4.16 Indications for carotid surgery.

History of ipsilateral carotid TIA or stroke with reasonable recovery
Severe stenosis (≥70%, NASCET method, excluding near-occlusion) and symptoms within 6 months
Moderate stenosis (50–69%, NASCET method) and symptoms within 2 months and male gender
Patients must be fit for surgery and an experienced, skilled surgical team available

NASCET, North American Symptomatic Carotid Endarterectomy Trial.

The benefits of surgery for carotid stenosis decline with time from symptoms to the operation. Patients with moderate degrees of stenosis (50–69%, measured using the NASCET method) benefit from surgery if it is performed within the first few weeks after recent symptoms, especially if they are male, but not thereafter. Patients with more severe stenosis may benefit from surgery performed up to 6 months after symptoms, but any delay in surgery in these patients will mean that some patients will already have had a stroke while awaiting surgery. It is therefore essential that patients should be referred as soon as possible after TIA and stroke for carotid investigations, and operated on as soon as possible if significant stenosis is detected. In patients with large acute infarcts, there may be a risk of causing reperfusion haemorrhage if the artery is operated on immediately, and it may be wise to wait 2 weeks or more before operating on these patients.

The main hazard of carotid endarterectomy is stroke during the procedure itself. There is also a small incidence of stroke in the first 2 weeks after endarterectomy, probably resulting mostly from a thrombus formed on the endarterectomy site. Surgery also risks MI, pulmonary embolism and the development of a haematoma at the wound site. Up to 10% of patients develop a cranial nerve palsy, usually a unilateral hypoglossal nerve palsy, but these usually recover and only rarely cause disability (Chapter 12). Performing the operation under local anaesthesia, rather than general anaesthesia, may avoid some of the complications of carotid endarterectomy, but this remains to be proven by ongoing trials. About 1% of patients develop hyperperfusion syndrome, which usually follows endarterectomy (or stenting)

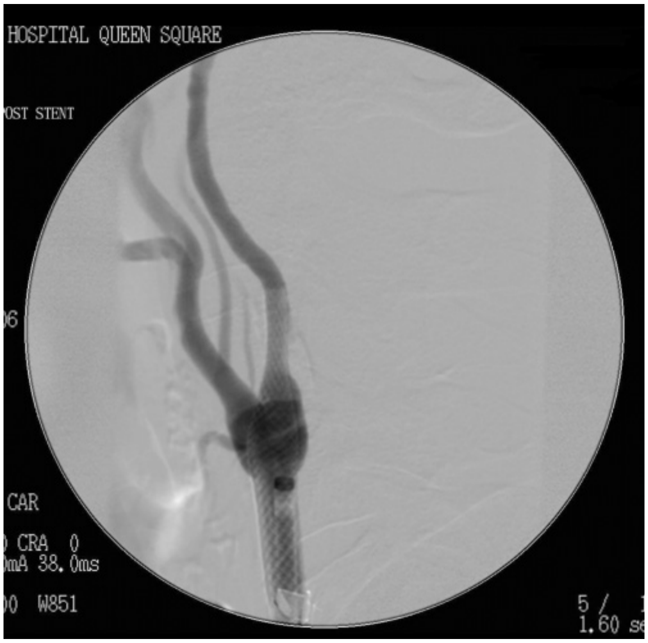

Figure 4.21 Stented left ICA stenosis; stent passes from common carotid artery (CCA) into internal carotid artery (ICA) (catheter angiogram).

for a very tight stenosis, and may be more common in patients who develop postoperative hypertension. Patients with hyperperfusion syndrome complain of headache and may develop seizures, and/or cerebral haemorrhage. Treatment of the hyperperfusion syndrome includes the urgent lowering of blood pressure.

Asymptomatic carotid stenosis

Patients investigated for TIA, stroke or other vascular conditions may be found to have a stenosis of one or more internal carotid arteries that is asymptomatic. A number of randomized trials have established that patients found to have carotid stenosis who have never had ipsilateral symptoms, or have had symptoms more than 6 months prior to randomization, have a very low rate of ipsilateral stroke during follow-up of around 2% per annum. Carotid endarterectomy for asymptomatic carotid stenosis is less hazardous than in symptomatic patients, but still carries a risk, in good hands, of around 3% within 30 days of the operation. Surgery then reduces the risk of ipsilateral stroke to about 1% per annum. The 5-year risk of any stroke or surgical death in the Asymptomatic Carotid Surgery Trial (ACST) fell from about 12% in patients in whom surgery was deferred until a more definite indication appeared (e.g. the stenosis became symptomatic), down to 6.4% in patients who had early endarterectomy. Subgroup analysis of ACST showed that patients over the age of 75 did not benefit from surgery, and the benefit in women was doubtful. The low rate of stroke in patients treated medically means that operating on asymptomatic carotid stenosis as a policy would result in a very large number of patients having unnecessary surgery, while some would be harmed from the operation, and only a small proportion (5%) would gain some benefit by avoiding stroke over the next 5 years. The majority of neurologists have concluded that this does not justify a policy of endarterectomy for asymptomatic stenosis, although exceptions may be made for young patients who are particularly anxious. The existing carotid endarterectomy trials did not incorporate state-of-the-art medical treatment. It is likely that in asymptomatic patients who are treated with high dose statins, have vigorous control of hypertension and stop smoking, the benefits of endarterectomy will be even less than those demonstrated in the trials. There is no benefit to following up asymptomatic stenosis with regular ultrasound examinations.

The benefits of carotid endarterectomy or stenting for patients with asymptomatic carotid stenosis who require major surgery, especially coronary artery bypass grafting (CABG), is uncertain. Severe carotid stenosis increases the risk of stroke during CABG, but the risk is not necessarily reduced by prior carotid endarterectomy or stenting, and the risk of stroke during treatment of the carotid artery are similar to the risk of stroke during CABG. Hence, a routine policy of screening and treatment of carotid stenosis prior to CABG is probably not justified. Patients who are symptomatic from both their carotid and coronary arteries should have the carotid treated prior to treatment of the coronary arteries.

Carotid stenting

Carotid stenting is rapidly developing as an alternative to carotid endarterectomy for the treatment of carotid stenosis. Carotid stenting has the advantage of avoiding any incision in the neck and is always performed under local anaesthesia. It appears less invasive and is therefore often preferred by patients to carotid endarterectomy, given the choice. However, the safety of carotid stenting compared to endarterectomy has not yet been established. The first trial of endovascular treatment for carotid stenosis compared to endarterectomy, the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) showed almost identical risk and long-term effectiveness of endovascular treatment compared with surgery, but did not include enough patients to form firm conclusions. Long-term follow-up from CAVATAS also showed a higher rate of restenosis in patients who received endovascular treatment compared to surgery, but this was not associated with a significant increase in the risk of stroke. Three other trials of carotid stenting have been stopped early because of poor results in stented patients, but this may reflect inexperience of the procedure in comparison to surgical skills in carotid endarterectomy, which have been developed over the last 50 years. Further randomized trials are in progress to compare carotid stenting with surgery, and until these are completed carotid endarterectomy should remain the treatment of choice for carotid stenosis, except in the context of clinical trials, or possibly in patients who have good indications for treating the carotid but are not fit for surgery, e.g. 'hostile neck' secondary to previous radiotherapy.

Vertebral stenosis

Vertebral artery stenosis is rarely treated by surgical methods because of difficulty with access. Stenting provides an alternative method of treating vertebral stenosis; this appears to be effective in preventing recurrent symptoms but is frequently associated with restenosis requiring further stenting or angioplasty. The benefits of vertebral stenting compared to medical treatment have not been established in clinical trials. We therefore reserve stenting for patients with vertebro-basilar symptoms associated with vertebral stenosis in the extracranial vertebral artery who have recurrent symptoms despite optimal medical treatment. Angioplasty and stenting are occasionally used to treat intracranial, vertebro-basilar and MCA stenosis, but treatment at this site has considerable hazards and is usually regarded as a last resort for patients with severe stenosis and recurrent symptoms unresponsive to other treatments.

Non-atherosclerotic vascular disease, and other rarer causes of stroke

Although the majority of patients with ischaemic arterial stroke and primary intraparenchymal haemorrhage have atherosclerosis, there are several important non-atherosclerotic vasculopathies, including extracranial arterial dissection and conditions associated with vasculitis.

Carotid and vertebral artery dissection

Cervicocephalic dissections should be especially considered in young patients. Although many disease processes that may be associated with dissection (e.g. Marfan's syndrome, Ehlers–Danlos syndrome and fibromuscular dysplasia), the vast majority occur in apparently normal subjects after trivial neck trauma, e.g. minor whiplash injuries or manipulation, or apparently spontaneously. New evidence is emerging that these people probably have subtle underlying collagen defects. These patients may have fragments of Marfanism. For example, they may be entirely double-jointed, or they may have a relative with Marfan's syndrome.

Fibromuscular dysplasia can affect many systemic arteries and is a non-atheromatous condition that may involve all three arterial wall layers. It is most commonly described in middle-aged women. Bilateral ICA involvement is common, sparing the bifurcation and intracranial carotid artery. In fibromuscular dysplasia, dysplastic fibrous tissue and proliferating smooth muscle cause constricting areas interspersed with areas of dilation. This is responsible for the characteristic sign on angiography – the 'string of beads' sign. Many of these lesions are benign or present with benign symptoms (e.g. pulsatile tinnitus) but stroke may occur from embolism or occlusion. The recurrence rate of stroke is low. In addition, patients with fibromuscular dysplasia have a high incidence of intracranial aneurysms and SAH.

In apparently spontaneous dissection, hyperextension of the neck during hairwashing in the salon or when painting a ceiling are common preceding events. Dissection is produced by the subintimal penetration of blood and subsequent extension between the vessel layers. This may lead to occlusion of the vessel but more often exposes a thrombogenic surface on which intraluminal haematoma develops. This haematoma may then embolize and produce stroke. The vast majority of cases affect the extracranial carotid and vertebral arteries. Intracranial dissection is much rarer but usually leads to SAH which is sometimes catastrophic. Occasionally, intracranial dissection cuts through perforating vessels and present as stroke.

The classic clinical scenario is of the precipitating event to be followed shortly by the development of neck pain and headache. There maybe a delay of several days, sometimes weeks before embolization causes stroke. Patients more often present when stroke has occurred. In some, dissection may never give rise to symptomatic embolization but in others dissection may be instantly associated with devastating cerebral infarction. Although any stroke syndrome may occur as a complication of dissection, the presence of a Horner's syndrome may be particularly alerting. In the carotid circulation, this will be caused by involvement of the ascending sympathetic fibres surrounding the ICA in the neck. In the vertebro-basilar circulation this may result from embolic occlusion of the posterior inferior cerebellar artery with resultant infarction of the dorsolateral medulla where the descending sympathetic tracts lie (lateral medullary syndrome). Some patients present with a painful Horner's syndrome alone brought about by carotid dissection. Occasionally, carotid dissection causes compression of a lower cranial nerve or nerves within the jugular foramen, e.g. a unilateral XIIth nerve lesion causing deviation of the tongue. MRI provides a sensitive and non-invasive means to confirm dissection. Fine-cut axial imaging through the neck may reveal the characteristic cresentic vessel wall haematoma and flow-related MRI (Figure 4.22). Catheter angiography may show tapering luminal compromise or, rarely, an intimal flap. Carotid imaging is far easier to interpret than vertebral imaging; as the vertebral artery is wrapped at some points in a venous plexus this sometimes give the artificial appearance of cresentic haematoma. The dissection should be followed on MRI as rarely a false aneurysm develops. These are usually asymptomatic but rarely may expand resulting in a retropharyngeal mass effect. Carotid ultrasound may show characteristic appearances, but is not as sensitive as other techniques.

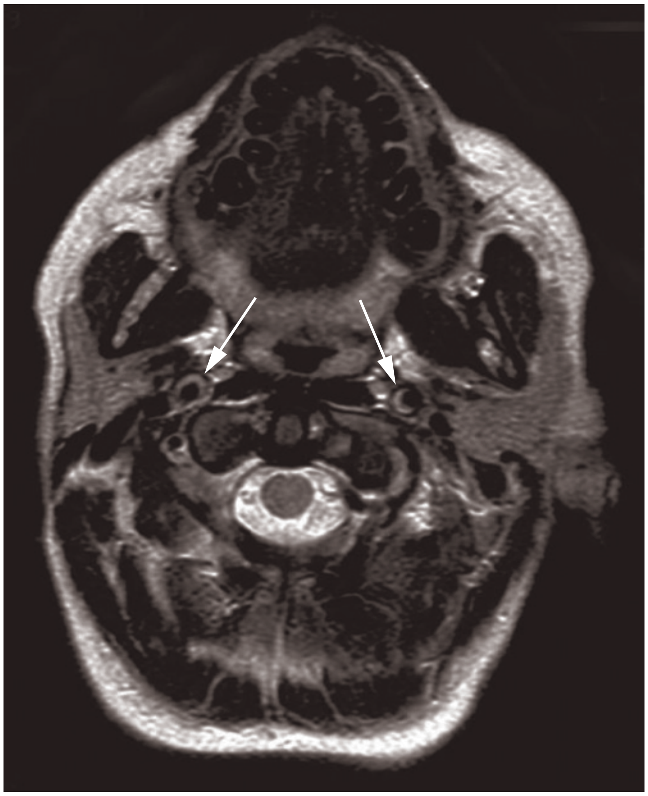

Figure 4.22 Bilateral internal carotid artery (ICA) dissection. Flow voids indicate patency of each arterial lumen; the crescent-shaped hyperintensity is the intramural thrombus on each side. (MRI T2W.)

The accepted management of dissection is anticoagulation with heparin, followed by warfarin for at least 3 months. The rationale is that anticoagulation will lower the risk of embolization. There is no clinical trial that provides solid evidence for this practice, but longitudinal studies show that stroke is rare following anticoagulation. There have been no randomized controlled trials comparing anticoagulation with antiplatelet therapy. There is no evidence that anticoagulation worsens intramural haematoma. In patients with false aneurysm formation, follow-up to ensure stability with MR angiography or ultrasound is recommended for 2 years. Expansions may need stenting.

Vasculitis

Vasculitis is beloved by some in the differential diagnosis of stroke. Although vasculitis may result in stroke (usually from uncontrolled hypertension), it is exceedingly rare for vasculitis to present simply as stroke. Vasculitis may be of infective origin, necrotizing, associated with collagen vascular disease, other systemic disease, hypersensitivity, giant cell or miscellaneous. Neurological investigations, other than the occasional cerebral biopsy, are not particularly helpful in the diagnosis of cerebral vasculitis. If MRI is requested with the words: 'Stroke – ? vasculitis', the report is likely to indicate: 'Vasculitis cannot be excluded'. In systemic and other vasculitides, the diagnosis is based on the extracranial features and typical serology. It is only when the vasculitis is confined to the nervous system (isolated angiitis) that the diagnosis will require more detailed investigation (see also Chapters 8, 25).

Infective vasculitis

Infective vasculitis associated with meningitis can occur acutely in the appropriate setting of severe bacterial, fungal, tuberculous or herpes zoster infection. There is nearly always an appropriate proceeding history suggestive of a menigo-encephalitis syndrome. After primary syphilis infection an obliterative endarteritis affecting the small vessels of the brain may occur with a usual latency of 7 years. Headache and encephalopathy predominate in the prodrome before stroke occurs. Evidence of previous infection is easy to screen for in the blood and those with neurological involvement usually have pleocytosis and positive serology in the CSF (Chapter 8). Enhanced MRI may show chronic syphilitic pachymeningitis with thickening of the meninges. Lyme borreliosis can mimic syphilis.

Viral infection may well be responsible for some cases of vasculitis previously considered idiopathic. Hepatitis B and C and herpes zoster are proven examples. Zoster is the most well-described form of viral arteritis to affect the CNS. The classic scenario is of V_1 shingles followed by brain infarction several weeks later. The infarct is usually ipsilateral to the rash and some patients may have encephalitis. The carotid territory is most commonly involved with occlusion at the siphon or MCA. In children, stroke may follow primary zoster infection (chickenpox). Patients with HIV have higher rates of cerebrovascular disease but there are many mechanisms underpinning this, including hypercoagulability.

Parasites may also be associated with endarteritis. Cysticercosis may be complicated by stroke when cysts lodge in the subarachnoid space leading to meningeal inflammation. The major basal arteries may be affected by this process and asymptomatic angiographic stenosis is more common than stroke.

In cerebral malaria caused by *Plasmodium falciparum*, haemorrhagic stroke may accompany the diffuse brain injury, particularly in children.

Systemic vasculitides

Systemic vasculitis has been classified immunopathologically, by the nature of the vessel involved or clinically. Most strokes associated with systemic vasculitis are brought about by uncontrolled hypertension, not cerebral involvement, and patients have usually been unwell for a considerable time. When looking at vasculitis through stroke spectacles, vessel size is a good starting point. Issues relevant to stroke are discussed here.

Large vessel vasculitis

These are Takayasu and giant cell arteritis. Both are granulomatous vasculitides. In giant cell arteritis (Chapter 25), the internal elastic lamina of the extracranial medium sized arteries becomes fragmented and invaded by inflammatory cells. It virtually always occurs in those aged over 50 and in 90% is accompanied by an elevated ESR. Patients complain of headache with scalp tenderness associated with malaise, depression, myalgia and sometimes claudication of the jaw muscles while eating. Examination usually reveals thickened tender temporal arteries. Stroke is a very rare complication of the disease but may occur from involvement of the extradural vertebral artery leading to brainstem infarction. A far more common complication without treatment, or at presentation, is anterior ischaemic optic neuropathy (Chapter 13). Diagnosis is established by temporal artery biopsy. Treatment is with high dose prednisolone, and if the diagnosis is correct the response of the systemic symptoms is dramatic and usually occurs within 1 day. Occasionally, the intracranial ICA may be involved.

Takayasu's arteritis was originally described in Japanese girls and women and is often called pulseless disease. There may be a prodromal phase associated with anaemia and raised ESR followed by severe occlusive disease of the aortic arch and branches, leading to absent neck and limb pulses. Stroke is not a common feature but headache, dizziness and syncope are more frequent. The diagnosis of Takayasu's arteritis may be made by ultrasound showing occluded or stenotic large vessels at the origin with thickened walls. Characteristic sites of involvement include the proximal common carotid artery (CCA), subclavian artery and innominate.

Medium vessel vasculitis

Polyarteritis nodosa (PAN) is the principle medium vessel vasculitis. It is important to remember that PAN is usually ANCA negative. PAN affects medium and small arteries and the most common neurological feature is mononeuritis. CNS involvement may occur in 20%, but it is often late in the disease. Presenting features include cerebral infarction, cerebral haemorrhage and SAH.

Small vessel vasculitis

Microscopic polyarteritis is usually ANCA positive and affects small vessels, as do Wegener's granulomatosis and Churg–Strauss syndrome. Encephalopathy and peripheral manifestations are common but stroke rare. Exceptional patients have presented with SAH as the first sign of vasculitis.

Collagen vascular disease

SLE commonly cause neurological problems. These are often neuropsychiatry and rarely caused by vasculitis. Encephalopathy, psychosis, seizures, stroke-like focal deficits, myelopathy and neuropathy are all encountered. At pathological examination the histology is often one of non-specific gliosis although thrombosis may be observed especially in those with antiphospholipid antibodies. Echocardiography shows a high frequency of valvular disease in SLE, particularly Libman–Sacks endocarditis, which may lead to cerebral embolism. Myocarditis is also a feature of SLE. Response to immunosupression of florid neurological involvement is often poor. Lupus may also cause a terminal carotid occlusive syndrome leading to a Moyamoya scenario.

Other vasculitis

Very rarely, true necrotizing arteritis can be seen in association with rheumatoid resulting in encephalopathy or small infarcts. Brain infarcts have also been reported in systemic sclerosis along with SAH, but there is a high incidence of hypertension in systemic sclerosis. Sarcoid may occasionally cause a cerebral vasculitis or focal infarction, usually in association with meningeal involvement.

Isolated angiitis of the central nervous system

This rare condition affects small and medium sized intracranial vessels. It may cause a combination of infarcts and haemorrhages. Presentation is usually chronic with prominent headache, leading to encephalopathy and then stroke-like focal dysfunction. Any age may be affected and there is a male predominance. The disorder may be acute over weeks or subacute. Angiography may reveal segmental narrowing of intracranial vessels but this is neither sensitive nor specific. Many patients have normal angiography. The CSF often shows a pleocytosis with oligoclonal immunoglobulin on electrophoresis. Brain imaging may show multiple small vessel infarcts and sometimes haemorrhages, if advanced. Diagnosis is by meningeal and brain biopsy, which typically shows a granulomatous vasculitis. If patients have neither headache nor CSF pleocytosis then biopsy rarely shows vasculitis. Treatment is with steroids and cyclophosphamide.

Thrombotic thrombocytopenic purpura

This is characterized by microangiopathic haemolytic anaemia, thrombocytopenia and systemic microinfarction from platelet-rich thrombi. Renal failure, fever and transient neurological signs, or diffuse encephalopathy are common. Large vessel infarction may also occur and cerebral haemorrhage. Posterior leucoencephalopathy has been described. The mainstay of treatment is plasma exchange but anticoagulation is sometimes necessary and the decision to do this has to be finely balanced against the risk of haemorrhage.

Behçet's disease

The common neurological manifestations of Behçet's disease are meningitis, encephalitis with multifocal signs, stroke-like events and dural sinus thrombosis. The lesions of Behçet's disease do not conform to arterial territories, suggesting a venous origin, and usually angiography shows no abnormalities. The brainstem is frequently involved.

Susac's syndrome

Susac termed this condition a microangiopathy of the brain and retina. The cochlea is also involved. There is always obliteration of the large retinal arteries causing severe progressive visual loss. Tinnitus and sudden hearing loss are common and the principle neurological features are dementia, pyramidal and cerebellar dysfunction. The disorder usually affects young women.

Sneddon's syndrome

This is characterized by chronic skin lesions, livedo reticularis and stroke. The most important feature is the livedo. Skin biopsy may show distinctive abnormalities in small and medium arteries. Cerebral angiography may show branch intracranial occlusions. APAS needs to be excluded.

Mitochondrial disease

MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) is sometimes considered as a differential diagnosis under the young stroke umbrella. Imaging may show multifocal abnormalities most often in the parieto-occipital and temporal lobes. Although the ischaemic lesions affect cortex and underlying white matter, these often cross arterial territories and the arteries supplying these areas are normal on investigation. Other features of a mitochondrial cytopathy are usually present (Chapter 9).

Fabry's disease

Fabry's disease is an X-linked lyposomal disorder in which there is deficiency of α galactosidase A. Typical clinical manifestations include painful neuropathy, stroke and renal failure, but young stroke may be the presenting feature. Angiography shows branch artery occlusion caused by the diffuse arteriopathy associated with sphingolipid accumulation. Imaging usually shows features of small vessel disease.

CADASIL

Of the rare conditions this actually does crop up from time to time in vascular clinics. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is a dominant condition characterized by migraine headache often with aura and extensive white matter abnormalities and lacunar infarction. Patients may present with depression, migraine, dementia and/or progressive gait difficulty. MRI often shows characteristic involvement of the temporal white matter. The diagnosis may be obtained through skin biopsy and genetic testing for the underlying mutation of the NOTCH III gene (Chapter 7).

Hypertensive encephalopathy

This condition, which is now rare, develops if systemic blood pressure exceeds the upper limit of cerebral autoregulation.

Oedema develops in the hyperperfused intracerebral circulation. Patients present with headache, fits, focal TIA-like events, stroke and depressed consciousness. Examination may reveal optic disc swelling in addition. The blood pressure is usually very high, e.g. 250/150 mmHg, but may be lower. In these patients the rate of blood pressure elevation has often been rapid and brought about by renal disease. Slower elevation allows autoregulatory mechanisms to compensate to some extent. Brain imaging may show a reversible posterior leuco-encephalopathy, as well as focal infarcts or haemorrhage. Eclampsia, in pregnancy and the puerperium, has similar features.

Migraine and stroke

There is a small but definite increase in stroke incidence in patients with migraine. However, this needs to be interpreted with caution as vascular disease predisposes to migraine headaches and aura. In particular, carotid artery dissection may precipitate a classic migraine attack with visual aura. There are links between antiphospholipid syndrome, sickle cell disease and possibly PFO with migraine, all of which can cause stroke. Other associations include mitochondrial disease and CADASIL. There remain very rare patients who develop infarction at the peak of a typical migraine attack, for which no other reason can be found. The symptoms of these migrainous strokes mimic the features of the patient's aura, and the associated infarction usually involves the occipital cortex. Hemiplegic migraine is a very rare familial channelopathy. Almost all young patients with migraine-like headache who suffer a hemiplegia have had the stroke from a cause unrelated to migraine. Migraine without aura, and more so migraine with aura, are both very slight independent risk factors for stroke (Chapter 11).

Moyamoya angiopathy

The term Moyamoya ('puff of smoke') angiopathy refers to an angiographic appearance in which terminal carotid occlusion is associated with the development of a fine and friable network of basal collateral vessels. Moyamoya disease is a distinct condition, prevalent in Japan but also occasionally seen in the West, in which a symmetric progressive and obliterative intracranial arteriopathy develops, affecting the basal vessels, usually the termination of both internal carotid arteries. The term Moyamoya syndrome is used when similar appearances, often with unilateral carotid occlusion, occurs from identifiable causes such as radiotherapy and sickle cell disease. Moyamoya disease presents most often in children as TIAs, stroke, chorea, headache or seizures. Adults more commonly present with ICH from rupture of the friable collaterals. Some patients appear to stabilize clinically in late adolescence, although long-term follow-up studies are lacking. Treatment options include surgical revascularization, either extracranial–intracranial bypass or synangiosis, a procedure in which vascularized omentum or muscle is juxtaposed to the brain. Children are usually prescribed aspirin, but this should be stopped in adults because of the risk of haemorrhage.

Cerebral venous thrombosis

Cerebral venous thrombosis is often considered under the umbrella of stroke but is a condition with diverse manifestations that mimic many other neurological disorders. It is increasingly recognized because of enhanced awareness and the use of MRI. Venous thrombosis may be septic or non-septic. Septic causes are increasingly rare but cavernous sinus thrombosis secondary to facial cellulitis and lateral sinus thrombosis secondary to purulent otitis media or mastoiditis are still seen. Septic thrombo-phlebitis of the cortical veins may also be associated with severe bacterial meningitis.

Aseptic thrombosis can affect the cortical veins, dural sinuses and deep veins. There are numerous potential causes. The most common are raised oestrogen levels in women, associated with pregnancy, the puerperium and the contraceptive pill. There are no reliable estimates of incidence although venous thrombosis may complicate 11/100,000 deliveries. Other factors include dehydration in association with systemic disease, thrombophilia (particularly the factor V Leiden polymorphism), activated protein C resistance and Behçet's syndrome. It has become clear that such external factors pose far more significant risk for recurrent thrombosis than inherited thrombophilias. In 20% of cases of venous thrombosis no aetiology is uncovered.

The clinical syndrome that manifests from cerebral venous thrombosis may be acute or subacute. The most frequent manifestations are headaches, seizures, altered consciousness, focal signs and optic disc swelling. Hence, cerebral venous thrombosis should be considered in the differential diagnosis of patients presenting with severe headache, seizure disorders, coma, stroke, acute meningo-encephalitis syndromes or isolated intracranial hypertension, mimicking idiopathic intracranial hypertension. Venous sinus thrombosis can cause headache, sometimes thunderclap, as the only feature. Only 50% of patients have papilloedema.

Venous thrombosis results in venous hypertension that leads to raised intracranial pressure. This may give rise to a syndrome of headache with papilloedema and normal CT imaging, initially identical to idiopathic intracranial hypertension. However, as the venous pressure rises, forced local arterial hypertension can lead to cerebral haemorrhage. Alternatively, or in addition, spread of the thrombus to cortical veins results in venous infarction, which is often haemorrhagic and results in focal neurological deficit and depression of consciousness.

Patients with venous sinus thrombosis may be severely ill and such patients often present to neurosurgeons as cases of primary intracerebral haemorrhage in coma. However, the radiological findings are usually distinct from both arterial ischaemic stroke and intracerebral haemorrhage. Venous infarction is characterized on imaging by vasogenic as opposed to cytotoxic oedema. These areas do not confine themselves to vascular territories and are often haemorrhagic. The thrombus in the venous sinuses may be visible on plain MRI although false negatives occur in the

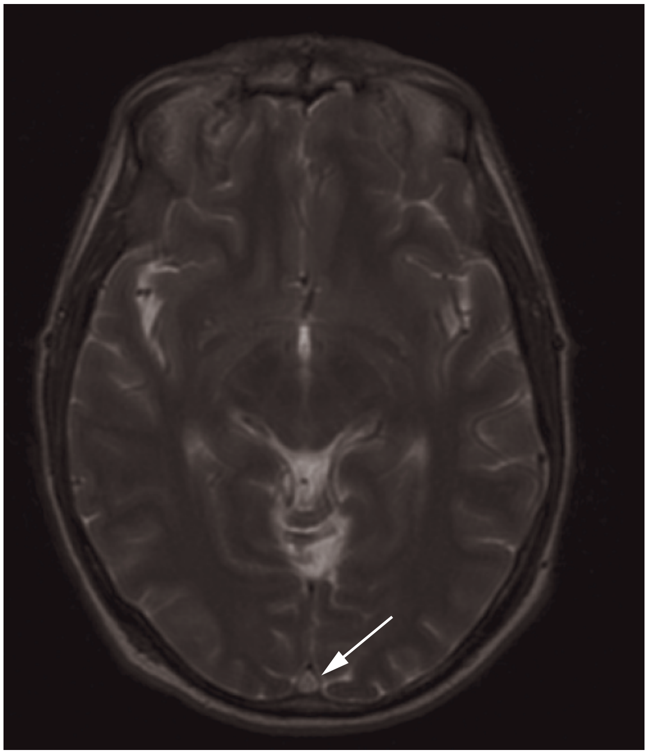

Figure 4.23 Absence of flow in the superior sagittal sinus caused by thrombus (MRI T2W). Arrow indicates thrombosed sagittal sinus.

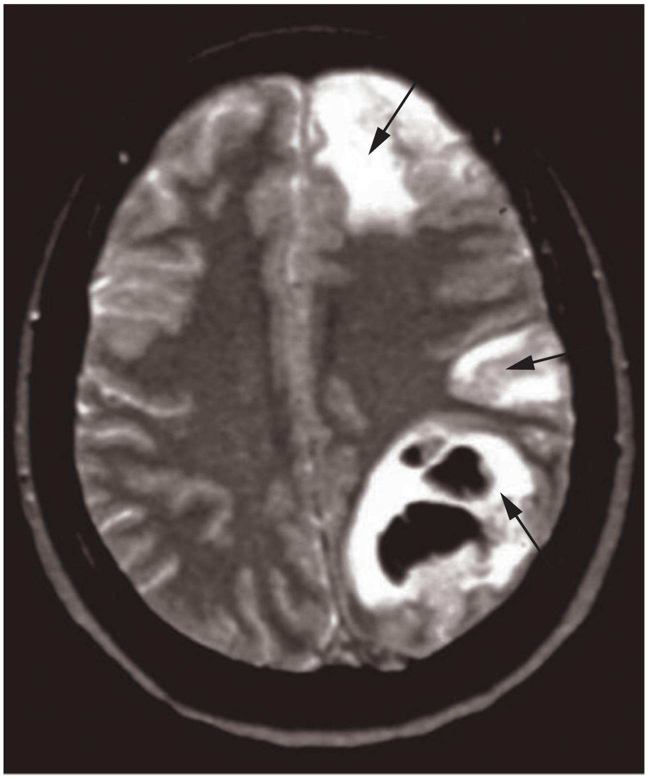

Figure 4.24 Parieto-occipital haemorrhage and multiple venous infarction (MRI T2W).

hyperacute (first few days) and chronic phases (1–2 months) necessitating flow-related imaging (Figure 4.23). Sometimes, the flow-related imaging can be difficult to interpret, especially whether the transverse sinus on the left is hypoplastic (a common variant) or thrombosed. If sufficient clinical suspicion exists and MR/MRV are negative, we recommend CT angiography or, if necessary, catheter angiography. Depending on local practice, CT angiography may be the investigation of choice. Rarely, venous sinus thrombosis is the result or the cause of dural fistulae and this often needs full intra- and extracranial angiography to diagnose.

The most common sinus involved is the sagittal sinus, followed by the lateral sinuses. Cortical veins may rarely be involved in isolation (Figure 4.24). Imaging proof of isolated cortical venous thrombosis is difficult. Often one has to embark on treament on the basis of the clinical presentation and MRI of a presumed venous infarct. Thrombosis of the deep venous system is rare in adults and gives rise to thalamic venous infarction with prolonged coma.

Cavernous sinus thrombosis should be considered a separate entity as it is most commonly caused by local sepsis rather than primary or secondary non-septic hypercoagulable states. It is a serious disease with a high mortality. The veins draining the face are the common portals, hence the view that facial cellulitis is a very serious condition. The early symptoms are pain, headache, fever, facial oedema then proptosis and ophthalmoplegia (Chapter 13). The principal treatment is antibiotics. Non-septic cavernous sinus thrombosis may follow head injury and thrombosis within dural cavernous arteriovenous fistulae. Cavernous sinus thrombosis rarely presents to stroke neurologists, but is seen more commonly in ophthalmological and emergency medical practice.

The accepted treatment of intracranial venous thrombosis is anticoagulation, whether haemorrhage is present or not. The evidence for this is controversial. Anticoagulants were first given to prevent pulmonary embolism from intracranial thrombosis. Early studies suggested that patients treated with anticoagulants had a 7% mortality as opposed to 37% untreated. A small prospective trial and retrospective analysis also suggested a significant survival benefit with anticoagulation and also the safety of heparin in the presence of haemorrhage. Later studies have suggested no advantage to heparin but were weighted toward less sick patients with indolent intracranial hypertension presentations, and better than expected outcomes in the placebo arm. It is the general view from clinical practice that anticoagulation is an essential treatment for these patients. The favoured method is subcutaneous low molecular weight heparin as opposed to intravenous heparin unless surgery is contemplated. The literature supports the safety of heparin in haemorrhage. In addition to anticoagulation, sepsis must be identified and treated with antibiotics and drainage where appropriate (e.g. mastoiditis). Patients with significant intracranial pressure will need ventilation and occasionally consideration for craniotomy. Our policy following venous thrombosis is to anticoagulate for 6 months, or for longer terms if a persisting reason for hypercoagulability persists. In patients with disc swelling vision should be monitored using a visual field screen (e.g. Goldmann) at regular intervals. Visual obscuration (Chapter 13) is a sign of incipient optic nerve infarction. Optic nerve fenestration, therapeutic lumbar puncture, lumbo-peritoneal shunting and acetazolamide all have their place in management. Recently, thrombolytic agents delivered by a transvenous endovascular route have been used to treat patients with sinus thrombosis and may be safe with haemorrhage. Early studies show promising results, but our current policy is to reserve this for patients not responding to, or worsening on, heparin.

The outcome of venous thrombosis tends to be polarized. Usually, patients either make a good recovery or die. Good outcome may be seen in up to 85%, death in 12%, and the remainder have an intermediate outcome. Mortality is higher with age and in association with infection or cancer. Seizures occurring during the acute phase have a good long-term prognosis with low rate of recurrence. Recurrent thrombosis may be seen in 10–20%, usually in the first year. The necessity for long-term anticoagulation after the first thrombosis is based on identifying ongoing active risk factors and the strategy is identical to that applied to limb venous thrombosis.

Vascular disease of the spinal cord

The spinal cord is most often affected by occlusion of the anterior spinal artery which supplies the anterior two-thirds of the cord. The blood supply is most tenuous in the upper thoracic region of the cord, which is a border-zone region. Although the anterior spinal artery is vulnerable to aortic dissection, most patients with anterior spinal artery occlusion presenting to a neurologist have atherosclerosis secondary to multiple risk factors, especially hypertension and diabetes. The dorsal columns are spared (because of a rich plexal supply) after the anterior spinal artery occludes. The resultant clinical picture is that of acute areflexic paraplegia characterized by dissociated sensory loss, with striking preservation of joint position and vibration sense but marked loss of pinprick and temperature sensation. Paraplegia is also well recognized following aortic surgery. There is a vogue still for anticoagulation of these patients but little evidence to support this measure.

The spine can also be affected by AVMs and dural fistulae. Dural fistulae present with symptoms resulting from venous hypertension and cord ischemia. Bleeding does not occur from spinal dural fistulae, unlike their cranial counterparts. They often present in elderly men with stepwise cauda equina symptoms with prominent exercise exacerbation. MRI virtually always shows dilated draining veins and treatment may be possible with embolization or surgery. The remainder of spinal AVMs are mostly intramedullary; they present in younger men with cord syndromes, cord or epidural bleeding. Treatment is often difficult, and unsatisfactory. Other features of vascular cord disease are discussed in Chapter 15.

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5 Movement Disorders

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Movement disorders are common causes of disability, especially in older people. They either cause poverty of movement, typical of akinetic-rigid disorders, or unwanted, involuntary movements – the hyperkinetic disorders, or dyskinesias.

Much early work in the field was pioneered by Dr Kinnier Wilson and Dr Purdon Martin at The National Hospital, and many others elsewhere. Professor David Marsden, in London and Professor Stanley Fahn (the Neurological Institute, New York) founded the Movement Disorder Society and its journal *Movement Disorders*.

Akinetic-rigid syndromes

Cardinal motor features of parkinsonism

Akinesia is the defining, obligatory and principal disabling feature of parkinsonism (Table 5.1). It is a symptom complex, comprising slowness of movement (bradykinesia), poverty of movement and small amplitude of movements (hypokinesia), difficulty initiating movement or with simultaneous motor acts and, most specifically, fatiguing and decrementing amplitude of repetitive alternating movements, which distinguish true akinesia from pyramidal or cerebellar slowing.

Almost all individuals with parkinsonism also display muscular rigidity to passive movement across a joint. Unlike spasticity, it is fairly equal in flexors and extensors, and may feel like bending a lead pipe; the presence of additional tremor (which may not be visibly evident) can add a ratchety 'cogwheel' feel to the rigidity (tremor alone can cause cogwheeling, but without rigidity).

Tremor is an optional extra for parkinsonism, and indeed for Parkinson's disease (PD) itself, although up to 80% of PD patients will display a tremor at some stage. This is usually in the form of a 4–6 Hz classic rest tremor which, in the hand, is 'pill-rolling' with flexion of the thumb. It typically subsides or lessens with movement, to reappear after an interval when a new position of rest (e.g. arms outstretched) is achieved ('re-emergent tremor'). A number of patients may additionally, or instead, display a faster postural tremor. A classic rest tremor, particularly if accompanied by a jaw tremor, is a strong pointer to PD or drug-induced parkinsonism, but this combination can also be seen in dystonic tremor (see tremor below). Classic rest tremor is uncommon, and jaw tremor rare, in other degenerative forms of parkinsonism.

To the above triad a fourth 'cardinal' motor feature of parkinsonism is sometimes added – postural abnormality. Flexed posture may or may not be evident early in the disease, and postural instability is typically a late feature in PD, so this item is not useful for detecting PD, although if present early on may point to alternative causes of the syndrome.

(Idiopathic) Parkinson's disease

Traditionally, PD has been defined as a clinico-pathological entity, in which progressive levodopa-responsive parkinsonism, without atypical features (see below), is associated, at autopsy, with neuronal loss and the presence of eosinophilic intracytoplasmic Lewy bodies in specific central and autonomic nervous structures. These include particularly the pigmented brainstem monoaminergic nuclei, the substantia nigra (dopaminergic) and locus caeruleus (noradrenergic). However, the pathology is usually much more widespread, also involving serotonergic raphe nuclei, dopaminergic mesolimbic, mesocortical and tubero-infundibular pathways, the cholinergic nucleus basalis of Meynert (NBM), cerebral cortex, the hypothalamus, the dorsal motor nucleus of vagus, the olfactory tract and sympathetic ganglia.

Clinical heterogeneity has long been recognized within 'PD', and the definition of PD has been turned upside down with the isolation (thus far) of two genes (*alpha-synuclein* and *LRKK2*), mutations in which (or, in the case of *alpha-synuclein*, duplications or triplications of which) can cause dominantly inherited or sporadic parkinsonism accompanied by Lewy bodies, and also

Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

Table 5.1 UK PDS Brain Bank diagnostic criteria for Parkinson's disease.

STEP 1. Diagnosis of a parkinsonian syndrome

Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) – obligatory

And at least one of the following:

- Muscular rigidity
- 4–6 Hz rest tremor
- Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction

STEP 2. Exclusion criteria for Parkinson's disease

History of repeated strokes with stepwise progression of parkinsonian features
History of repeated head injury
History of definite encephalitis
Oculogyric crises
Neuroleptic treatment at onset of symptoms
More than one affected relative
Sustained remission
Strictly unilateral features after 3 years
Supranuclear gaze palsy
Cerebellar signs
Early severe autonomic involvement
Early severe dementia with disturbances of memory, language and praxis
Babinski sign
Imaging evidence of a cerebral tumour or communicating hydrocephalus
Negative response to large doses of levodopa if malabsorption excluded.
MPTP exposure

STEP 3. Supportive prospective positive criteria for Parkinson's disease

(Three or more required for diagnosis of definite Parkinson's disease)
Unilateral onset
Rest tremor present
Progressive disorder
Persistent asymmetry affecting the side of onset most
Excellent response (70–100%) to levodopa
Severe levodopa-induced chorea
Levodopa response for 5 years or more
Clinical course of 10 years or more

Table 5.2 Causes of parkinsonism and other conditions sometimes confused with Parkinson's disease.

Idiopathic Parkinson's disease (including DLB)

Genetically determined 'Parkinson's diseases'

Dominant

- *Alpha-synuclein* mutations (PARK1) or gene duplications/ triplications (PARK4)
- *LRKK2*/dardarin mutations (PARK8)

Recessive

- *Parkin* mutations (PARK2)
- *DJ1* mutations (PARK7)
- *PINK1* mutations (PARK6)

Other neurodegenerative diseases

Classically sporadic

- Multiple system atrophy (MSA)
- Progressive supranuclear palsy (PSP)
- Cortico-basal degeneration (CBD)

Genetic

- Dominant
  Huntington's disease (HD, Westphal variant)
  Spinocerebellar ataxia type 2 (SCA2)
  SCA3
  Frontotemporal dementia with parkinsonism related to chromosome 17 (FTDP-17)
- Recessive
  Wilson's disease (WD)
  Neurodegeneration with brain iron accumulation (NBIA) type 1 (formerly Hallervorden–Spatz disease)
- Uncertain
  Parkinsonism–dementia–ALS complex of Guam
  PSP-like atypical parkinsonism in Guadeloupe
- Other genetic
  Dopa-responsive dystonia (DYT5, Segawa disease – older patients) – dominant with incomplete penetrance
  Dystonia-parkinsonism in Filipinos (DYT3, XDP,Lubag) – X-linked
  Rapid onset dystonia-parkinsonism (DYT12) – dominant
- Reversible drug-induced secondary to dopamine receptor blocking or dopamine depleting drugs
- Toxic, due to MPTP/CO/methanol/manganese
- Post-encephalitic due to encephalitis lethargica/post-strep/Japanese B encephalitis
- Dementia with Lewy bodies (DLB)
- Vascular parkinsonism/pseudoparkinsonism*
- Post-traumatic due to repeated head trauma ('punch-drunk syndrome') or midbrain compression
- Essential tremor*
- Dystonic tremor*

* Often misdiagnosed as Parkinson's disease even though fatiguing/decrement of repetitive movements not present.

three recessive genes (*parkin*, *DJ1* and *PINK1*), mutations of which can cause parkinsonism, typically without Lewy bodies, mainly in younger individuals. Thus, there are at least six 'PDs' so far, with perhaps a dozen or more yet to identify. How many of these should still be called Parkinson's disease is a moot point. The phenotypes of these monogeneic 'PDs', especially of *LRKK2* cases, can be indistinguishable from typical sporadic PD. However, patients with *alpha-synuclein* mutations or triplications have somewhat younger onset, shorter survival and a higher incidence of dementia. The recessive forms have younger onset, slower disease progression and present with leg tremor more often than sporadic PD.

Molecular advances have introduced alternative schemata for classifying the principal degenerative parkinsonisms into alpha-synucleinopathies (Lewy body diseases and multiple system atrophy [MSA]), tauopathies (including progressive supranuclear palsy [PSP] and cortico-basal degeneration [CBD]), and others (e.g. cases with parkin mutations). Classification is therefore currently back in the 'melting pot'. Table 5.2 gives causes of parkinsonism and other conditions sometimes confused with PD.

The prevalence of PD in most countries is around 180/100,000. Different genetic causes vary in frequency in different populations (e.g. *LRKK2*-related parkinsonism is particularly common in Askenazi Jews and in North Africans). Overall, incidence rises steadily with age, although recessive forms become less frequent with age. Average age at onset is about 60 years, with fewer than 5% of cases starting before age 40. Despite modern treatment, life expectancy is still reduced, with a standardized mortality ratio of about 1.9.

The most widely used clinical diagnostic criteria for PD are still those elaborated in 1988 by the UK Parkinson's Disease Society Brain Bank (Table 5.1).

PD has been traditionally defined as a motor disorder, but the frequency and importance of premotor and non-motor features is increasingly recognized.

Premotor features

All neuronal systems have built-in reserves in terms of tolerating a degree of neuronal loss, and compensating for this by up-regulation of surviving neuronal function before a threshold symptomatic deficit is reached. Thus, 60–80% of nigro-striatal dopaminergic reserve is lost before the motor features of parkinsonism emerge. Brains with 'subclinical' nigral Lewy bodies have been called 'incidental Lewy body disease'. Sequential fluorodopa positron emission tomography (PET) scans have been used to estimate, by back-extrapolation, the duration of the 'presymptomatic' phase of PD, with estimates varying between 3 and 6 years. However, a number of pathological and clinical observations have questioned this. Thus, in 2006, Braak *et al.*, based on examination of Lewy body pathology in a large number of brains of individuals with and without clinical parkinsonism in life, postulated 6 'stages' of PD. In stages 1 and 2, Lewy bodies are restricted to the medulla, pontine tegmentum and anterior olfactory structures, and it is only in stage 3 that the nigro-striatal tract is first involved. Thus, back-extrapolation from fluorodopa PET scans can only, at best, tell us when stage 3 might begin. Clinically, constipation, dysphagia, olfactory impairment, cardiovascular autonomic involvement and REM sleep behaviour disorder (RBD) can precede, by many more years, the appearance of the motor disorder in PD. In RBD there is loss of the usual somatic atonia that accompanies dreaming, such that the individual is able to 'act out' usually frightening dreams, often striking or injuring their bed-partner, and often with vocalizations. In one sleep laboratory study, 38% of 29 men with (at that time idiopathic) RBD went on to be diagnosed with a parkinsonian disorder an average of 3.7 years after the diagnosis and 12.7 years after the onset of their RBD.

When candidate neuroprotective agents do appear, if they are to be applied to greatest effect they will need to be given as early in the disease process as possible, hence the considerable current efforts to develop a reliable battery of tests to screen for subjects in the earliest stages of disease, or with a particularly high risk.

Other non-motor features

A host of other non-motor features occur in, and can be the most disabling features of PD:

- Sialorrhoea is particularly a problem in later disease; only a few patients can tolerate centrally acting anticholinergics such as scopolamine because of the risk of confusion, but some can be helped by peripherally acting drugs, or botulinum toxin injections or radiotherapy to salivary glands.
- Drenching sweats usually occur in drug-treated patients, but are poorly understood and no effective pharmacological treatment exists.
- Urinary urgency and frequency are common, as a result of detrusor hyper-reflexia in PD, and can be helped by a peripherally acting anticholinergic such as trospium.
- Depression, usually minor rather than major, affects about 40% of patients before, at or after diagnosis. The symptomatology of this minor depression overlaps with abulia, and lack of initiative and drive, which is also common in PD. Clinical depression is probably best treated with a selective serotonin re-uptake inhibitor (SSRI) rather than a tricyclic. In numerous studies, depression has been shown to be the most important factor correlating with impaired quality of life, so it should be actively sought, and treated if found.
- Anxiety, and sometimes panic, can also be a major problem for many patients, and again is poorly understood.
- Pain is also common in PD. It may be a presenting feature or may arise in established disease.

Any or all of the features described here may occur not on a sustained basis, but appear at times when the patient is 'off' or wearing off in the context of levodopa-related motor fluctuations – indeed, such *non*-motor fluctuations can represent the patient's biggest problem. Pain is typically lateralized to the side more affected by PD. Appropriate management in these patients may take the form of measures to minimize time 'off', e.g. by appropriately timed injections of apomorphine, rather than necessarily resorting to antidepressants or analgesics.

A whole range of neuropsychiatric disturbances resulting from the disease or its treatment can also occur (see below).

The 'typical' motor presentation of PD

PD is classically an asymmetric disease, remaining so throughout its course. It more commonly starts in the arm, with impaired dexterity on fine tasks, and often with a tremor at rest, e.g. holding a newspaper. Other patients present with a tendency to drag one leg or shuffle. The spouse may have noticed a general slowing down, a change in facial expression or impaired arm swing. Direct questioning may reveal a change in voice or micrographia, but speech difficulty or micrographia as presenting complaints are less common, raising the possibility of atypical disease. The patient may admit to aching or sometimes pain in the affected limb, and presentation with or development of a frozen shoulder or worsening back discomfort is well recognized.

Examination will reveal akinesia, usually with rigidity and often tremor, which may be difficult to bring out. The patient should be asked to dangle the wrists over the arms of a chair, and stressed by being asked to count backwards with the eyes closed, again with the arms outstretched, then with the fingers in front of the nose. Often the earliest tremor to be observed may be an adduction–abduction tremor of the fingers. Sometimes, the only time a rest tremor is observed is on walking, when reduced arm swing, flexed posture (initially of one arm) and gait abnormality may be seen.

Atypical features should also be sought. The 'bedside' examination of eye movements should be normal (except for some limitation of convergence or of up-gaze with normal saccadic velocity), and there should be no evidence of limb or gait ataxia or dysdiadochokinesis, no apraxia and no pyramidal signs. The so-called 'striatal toe' can mimic a Babinski response, but is often present spontaneously or on walking and is not accompanied by other pyramidal features. Sometimes (particularly younger) patients may present with 'dystonic claudication' (exercise-induced leg dystonia) on prolonged walking. Early postural stability or freezing of gait, although sometimes seen in PD, should raise other possibilities. Of note, patients who are unsteady for whatever reason may not swing their arms, and abnormal arm swing is also common in patients with dystonia.

Evolution of disease

Unilateral PD (stage 1 on the non-linear Hoehn and Yahr scale) always progresses, through stage 2 (bilateral), which typically lasts for 5–10 years, until postural instability (stage 3) appears. Over time, fully developed disease (stage 4) develops, and after many years the patient may eventually become chair- or even bedbound (stage 5). However, this progression is influenced by treatment, so that a patient on chronic levodopa treatment may fluctuate between stage 4 or even 5 when 'off', to stage 2 or 3 when 'on'. Freezing of gait is usually a late feature.

Ancillary investigations

Young onset (less than 40 years) patients should always be screened for Wilson's disease with serum copper and coeruloplasmin and slit-lamp examination. Routine magnetic resonance imaging (MRI) of the brain is normal in PD and not necessary in typical cases. A dopamine transporter (DaT) single photon emission computerized tomography (SPECT) scan can sometimes be useful to confirm a nigro-striatal lesion (see further details below) but in a typical case of PD is unnecessary and expensive.

Treatment

Discussion of treatment options is influenced by what is known about the course of PD on chronic treatment with levodopa preparations, so levodopa will be dealt with first, 'out of turn', in order to inform about alternative treatments early in the disease course.

Levodopa

Preparations of levodopa combined with the peripheral decarboxylase inhibitors (PDIs) carbidopa or benserazide (co-careldopa, Sinemet; co-beneldopa, Madopar) are still the most potent and effective symptomatic treatment for PD, and remain the 'gold standard'. Levodopa, in common with other large neutral amino acids, is transferred across the wall of the proximal small bowel, and again across the blood–brain barrier, by a competitive active transport system. Some patients find that protein in meals impairs the effect of a dose of levodopa close to meals, so that timing or size of the dose, or the protein intake, may need adjustment.

Once in the brain, no longer protected from the peripheral decarboxylase inhibitor that cannot follow it, levodopa is metabolized to dopamine, which then stimulates available dopamine receptors in striatum (but also elsewhere in the brain).

It is usual to start with half a tablet of 25/100 (PDI/levodopa) strength b.d. or t.d.s. for a couple of weeks, then doubling the dose and waiting to judge the effect. If ineffective or insufficiently effective, the dosage may then be increased to 1½ or 2 tablets t.d.s., although the ELLDOPA trial showed increasing rates of dyskinesia and wearing-off, particularly as the dose increased from levodopa 300 to 600 mg/day. Almost all PD patients will show marked improvement at this dose but, if ineffective, the total daily dosage of levodopa should be further increased to 1–1.5 g/day (if tolerated) before deciding it is not going to benefit a given patient. One should note that there are long duration effects of levodopa such that a treatment change can take at least 2 weeks for its effect to equilibrate in the brain, and similarly one can see late deterioration up to 2 weeks after discontinuing or reducing the dosage. Initially, benefit is smooth throughout the day, even if a dose is late or missed – the so-called 'honeymoon period'. Over time, however, patients start to notice early morning akinesia, or wearing off of their doses, and around the same time develop an 'overshoot' from akinesia to dyskinesia when the dose is working. A very rough rule of thumb is that these problems (the long-term levodopa syndrome) develop in 10% of patients per year of treatment, so that after 5 years about 50% of patients will have them, and after 10 years all patients will ultimately experience them, to a greater or lesser degree. In general, younger onset patients develop them earlier and to a more severe degree. Rates reported from clinic-based series are higher than those in community-based studies.

Gradually a 'threshold' level of dopaminergic transmission in the striatum develops, so that the doses work in an all-or-none fashion, and the patients fluctuate, sometimes over minutes or even seconds, from mobile dyskinetic 'on' to akinetic 'off'. Fractionation of doses to give smaller amounts more frequently may lead to dose failure, or unpredictability of effect. This may also occur with controlled release (CR) preparations because, relative to standard preparations, bioavailability of CR levodopa is only 70%; moreover, although providing a longer tail at the end of the dose, CR is absorbed more slowly than standard, leading to delayed 'on' and sometimes only a short 'on' period because the threshold is only briefly exceeded. CR formulations have been disappointing in managing daytime fluctuations, but useful at bedtime to improve nights. A (very expensive) levodopa-carbidopa gel (Duodopa) delivered continuously into proximal jejunum via a gastrostomy can give stable plasma levels and improve fluctuations in patients who are unsuitable for, or unable to tolerate, apomorphine or surgery.

Mobile dyskinesias can be peak dose (occurring mainly at the peak of action of each dose), square wave (occurring throughout the period of benefit) or diphasic (being much more severe at the beginning or at the end of action of a dose of levodopa). Most 'on' period dyskinesias are usually a mixture of chorea and dystonia, but when diphasic (usually in young onset patients) they can be violent and disabling stereotyped or ballistic movements.

Some patients develop 'off' period dystonia, which is relatively fixed, usually painful, most commonly affects one leg and relates to falling, low or intermediate levels of dopaminergic stimulation; paradoxically, they are both caused and relieved by levodopa, disappearing when the patient turns 'on'. Levodopa-induced dyskinesias in PD typically involve limbs more than neck and face, and are more severe on the initially, and more, affected side.

Other side effects of levodopa

Levodopa can also cause nausea or vomiting, mainly by stimulating dopamine receptors in the chemoreceptor trigger zone in the area postrema in the floor of the fourth ventricle, functionally outside the blood–brain barrier, which can be prevented or reduced by giving domperidone, a peripheral dopamine antagonist that does not follow levodopa into the brain. Levodopa can also cause or aggravate postural hypotension, mainly through a central action. It can also cause a wide range of neuropsychiatric disturbances in susceptible individuals.

There is no evidence that levodopa kills nigral dopaminergic neurones in patients with PD. However, concerns about the development of the long-term levodopa syndrome have led many physicians to try to delay the introduction of levodopa, if possible, at least in younger patients, by using a variety of medications that do not cause this problem, although at the expense of having a less potent therapeutic effect and more psychiatric adverse effects.

When to start treatment

No drug has so far been proven to be neuroprotective in PD. When the patient is first diagnosed they may not feel in need of symptomatic treatment, and the doctor may not wish to rush into treatment at the first visit. There have been recent suggestions that early initiation of treatment might improve subsequent response, even without a neuroprotective action, but this is unproven. Today, most physicians still wait until the patient's symptoms are beginning to affect their daily life before starting symptomatic treatment.

How to start treatment

There is little to be gained in elderly PD patients, especially if cognitively impaired, in using alternative medications to delay the introduction of levodopa, because in this group it has the best therapeutic index – other drugs, and polypharmacy, are more likely to produce confusion or hallucinations, while also being clinically less effective.

In contrast, in younger patients there are several possible options.

Catechol-O-methyl transferase (COMT) inhibitors

Entacapone (peripheral) and tolcapone (peripheral and central COMT inhibitor) block the conversion of levodopa to 3-O-methyldopa, its principal metabolite. They both extend the elimination half-life of levodopa, and thereby often extend the duration of action of individual doses. Tolcapone is generally the more effective of the two, but is only used as a second-line treatment because of a (low) risk of potentially fatal hepatotoxicity, necessitating frequent liver function test monitoring. Both drugs can cause gastrointestinal upset, particularly diarrhoea, and a harmless orange discoloration of the urine. A combined tablet containing levodopa, carbidopa and entacapone (Stalevo) is available.

Monoamine oxidase B (MAO-B) inhibitors

Selegiline and rasagiline are 'suicide' inhibitors of MAO-B, the iso-enzyme responsible for catabolizing dopamine to homovanillic acid (HVA). Unlike MAO-A inhibitors, they can safely be given together with levodopa. Used alone in early disease, these drugs can, probably through a mild sympathomimetic effect, delay the need for levodopa. Oral selegiline is partly metabolized to metamphetamine, so should be given in the morning to avoid insomnia. Zelapar, a buccally absorbed preparation of selegiline, avoids first-pass metabolism and hence this problem. Otherwise these drugs have very few side effects when given alone, but can potentiate any of the symptomatic side effects of levodopa.

Anticholinergics

Anticholinergics were the first drugs used to treat PD. They usually have only a mild symptomatic effect, often restricted to reducing tremor, although when abruptly discontinued patients can dramatically worsen acutely. Because of cortical pathology, and the cholinergic deficit caused by NBM pathology, older PD patients are particularly susceptible to develop hallucinations and organic confusional states when given centrally acting anticholinergics, so these should be avoided in such cases, and restricted to younger, cognitively intact, usually tremor-dominant patients.

In the periphery, anticholinergics can cause blurred near vision because of mydriasis (so are contraindicated in narrow angle glaucoma), delayed gastric emptying and constipation. However, they can help sialorrhoea, and also reduce the detrusor hyperreflexia commonly responsible for frequency and urgency in PD, but can precipitate retention of urine if there is also an element of prostatic obstruction.

Amantadine

This drug has several actions: an amphetamine-like effect (releasing presynaptic dopamine stores); a mild anticholinergic effect; a mild dopamine re-uptake inhibition effect; finally, it is also an *N*-methyl-D-asparate (NMDA) glutamate receptor antagonist.

Traditionally, amantadine was used as a mild early treatment. Often the effect would wane, at least in part, after 6 weeks or so. The drug commonly causes ankle oedema and livedo reticularis, and lowers seizure threshold. It can cause hallucinations or confusion, and is excreted by the kidneys, so should be used with caution in renal failure. More recently, amantadine has been recognized to have a (sometimes dramatic) antidyskinetic effect in at least some patients on levodopa, without worsening parkinsonism, presumed to be mediated by its NMDA antagonist property. It can also help freezing, even 'on' freezing, in a minority of patients.

Dopamine agonists

Dopamine agonists stimulate dopamine receptors directly. Six oral agonists (four ergoline: bromocriptine, lisuride, pergolide and cabergoline; and two non-ergoline: ropinirole and pramipexole) and one transdermal non-ergoline agonist (rotigotine) are available. Given before levodopa is introduced, these drugs cause fluctuations and dyskinesias much less frequently, but have a weaker antiparkinsonian effect. However, they can cause dyskinesias in patients who have already developed them on chronic levodopa treatment. The intensity of dyskinesias in levodopa-treated patients can often be lessened by partially replacing levodopa with an agonist.

Adverse effects

Dopamine agonists stimulate both peripheral and central dopamine receptors. The risk of nausea and vomiting can be reduced by the peripherally acting dopamine receptor antagonist domperidone, which does not cross the blood–brain barrier. Other antiemetics that do not block dopamine receptors are cyclizine, promethazine and ondansetron. Tolerance to nausea usually develops rapidly over 10 days or so, and there is cross-tolerance between levodopa and agonists, and between different agonists. Covering the introduction of an agonist is therefore most important with *de novo* treatment, optional when adding an agonist to levodopa, and unnecessary when switching between agonists (except to switch to apomorphine).

Agonists can cause postural hypotension and aggravate active cardiac disease or peptic ulceration. Any antiparkinsonian medication can cause neuropsychiatric adverse effects, but the oral agonists definitely cause more problems than levodopa. At the milder end of the spectrum, they can cause vivid dreams or nightmares, illusions, extracampine hallucinations (delusions of presence) or (typically visual) pseudohallucinations (with retained insight), of animals or people, sometimes Lilliputian, often non-threatening. More problematic are true hallucinations (with loss of insight) and other delusions (often paranoid, sometimes involving morbid jealousy); and hypersexuality, exhibitionism or paraphilia and pathological gambling and shopping (sometimes isolated, but sometimes in the context of hypomanic-like symptoms), and 'punding' (defined as repeated stereotyped pointless complex behaviours), often grouped together under the heading of impulse control disorders or dopamine dysregulation syndrome.

All agonists can cause ankle swelling, sometimes extending to the knees or higher. In most cases the mechanism is unknown, but evidence of cardiac failure should always be sought. The ergot derivatives, particularly, can cause a tense angry erythematous rash called erythromelalgia.

It has long been recognized that some agonists can (rarely) cause lung fibrosis, pleuro-pulmonary effusions or (even more rarely) retroperitoneal fibrosis. More recently, they have also been found to cause fibrosis of heart valves (most commonly the tricuspid), analogous to what is seen with carcinoid tumours and fenfluramine treatment. This reaction is thought to be mediated by stimulation of 5HT2B receptors, and to be wholly, or mostly, restricted to ergoline agonists. The vast majority of patients found on echocardiography to be affected are asymptomatic, but because of these problems pergolide is being withdrawn by the manufacturers in the USA, and cabergoline might follow suit.

de novo use of dopamine agonists

Patients should be warned that at low dosage dopamine agonists can have a paradoxical effect of worsening parkinsonism. This is because the presynaptic dopamine D2 autoreceptors that shut down endogenous dopamine release are more sensitive to dopamine agonists than are the postsynaptic D2 receptors that mediate their beneficial motor effects. Agonists are often used in suboptimal dosage, often because the patient stops increasing the dosage at the end of a 'starter pack', and because of confusion about what is meant by 'minimum effective dose' – this may be construed as the dose that is effective, but is usually the minimum dose that has any useful effect.

If an agonist has not been effective, or not well tolerated, what should be done? This partly depends on the dosage reached. The authors' practice is that if a patient achieves up to two-thirds of the recommended dosage with absolutely no benefit, usually either levodopa is added or, less often, another agonist is used instead. If the patient benefits, but not sufficiently, upward titration towards the maximum dosage would be used, side effects permitting, before adding levodopa and later cutting back on the agonist dosage. If one oral agonist fails to have any useful effect at maximum dosage, there is usually little to be gained by switching to another. If one agonist is poorly tolerated because of somnolence, one may switch to another, although risking the same problem again. If an agonist is poorly tolerated because of hallucinations, delusions or confusion, there is a significant risk of the same with another agonist.

'Add-on' use of dopamine agonists

Dopamine agonists have longer clinical and pharmacological half-lives than levodopa. Hence, when added, they can help to minimize 'troughs' of dopaminergic stimulation and increase 'on' time. Dyskinesias will usually increase, unless the dose of levodopa is reduced to compensate. In general, the less a patient's dopaminergic stimulation is obtained from levodopa and the more from an agonist, the less severe their dyskinesias tend to be.

Apomorphine is the oldest and most effective agonist. Because of extensive first pass metabolism, it has to be given parenterally, by subcutaneous intermittent injection, to 'rescue' patients from 'off' periods, or by continuous infusion to reduce them. The effect of single injections (usually 3–5 mg) is rapid (within 10–15 minutes) and reliable. Infusions (usually 3–6 mg/hour) can be supplemented by on-demand boluses. Apomorphine causes more drowsiness, particularly initially, and less psychiatric morbidity than oral agonists. It can rarely cause an autoimmune haemolytic anaemia, so periodic haemoglobin, reticulocytes and Coombs testing is mandatory. Patients may also develop tender, inflamed or infected subcutaneous nodules or panniculitis which may cause them to abandon treatment. Infusions are usually given for about 12 hours during the day, and any oral agonists can usually be tailed off and levodopa dosage often reduced. Dyskinesias usually diminish over weeks or months. Some patients use apomorphine infusions just at night, or 24 hours/day, with a lower rate at night. Occasional patients who are very sensitive to levodopa may end up on apomorphine monotherapy.

Surgery for PD

For some patients with advanced PD, with motor fluctuations and dyskinesias, or troublesome tremor, who are difficult to manage despite the combination of available drugs, functional neurosurgery can be an option. Lesioning procedures were applied for many years but have been largely replaced by deep brain stimulation (DBS) in most countries. DBS uses permanent implanted electrodes in the brain in conjunction with a pacemaker that delivers high-frequency electrical impulses. The three established brain targets for the treatment of PD with DBS are the ventrolateral thalamus, the internal pallidum (GPi) and the subthalamic nucleus (STN). DBS on each target improves a different range of symptoms.

Thalamic deep brain stimulation

Thalamic stimulation was developed in 1987 to treat tremor related to PD or essential tremor, initially contralaterally to a previous thalamotomy. In view of the benefits on tremor and the low rate of side effects, bilateral thalamic stimulation was then performed. However, thalamic DBS does not allow much reduction in drug dosage. Balance problems and dysarthria are possible side effects, especially after bilateral surgery. Patients are usually asked to stop the stimulation at night to reduce the risk of tolerance and rebound. Benefits on tremor can be maintained for more than 10 years. Nevertheless, some long-term studies have shown that in many patients other symptoms such as gait difficulty and dyskinesia progress and are not helped by thalamic DBS. This has lead to the search for other brain targets in which DBS may help those symptoms and there has been a decrease in the indications for thalamic DBS. Thalamic DBS still has a place for elderly patients with tremor dominant disease.

Subthalamic nucleus deep brain stimulation

Subthalamic nucleus deep brain stimulation (STN DBS) was developed in 1993, following basic research in the MPTP monkey model of PD. Hyperactivity of the STN was identified in their parkinsonian condition and an improvement of symptoms after STN lesions. In patients with PD, STN DBS can improve a large range of off-phase symptoms: limb bradykinesia, rigidity, tremor and gait difficulty including balance and freezing (if they are also dopa-sensitive). Levodopa-induced dyskinesias also improve over time, probably largely because of drug dosage reduction. 'Off' dystonia improves as well. Dopa-refractory symptoms are not helped and the effect on speech is variable, and in some patients intelligibility can deteriorate. Medications are usually reduced after STN DBS. In the early stage, stimulation is increased slowly in parallel with drug reduction to avoid increase of dyskinesias. After 5 years of STN DBS, although some of the benefits are maintained, the effect on axial features and the on-phase scores often declines. Side effects are not infrequent; they include speech problems, neuropsychiatric problems (in particular mood change), eyelid opening apraxia and dyskinesias induced by the stimulation.

Internal pallidum deep brain stimulation

Internal pallidum (GPi) DBS was developed in parallel with STN DBS but a smaller number of patients have received surgery because most teams opt for STN DBS. The effect on 'off' symptoms is more variable than with STN, the most reliable effect being against dyskinesia. Nevertheless, preliminary results of a comparative study have shown only a moderate difference between the results of GPi versus STN DBS. GPi DBS nevertheless has the advantage of a lower rate of side effects and remains useful particularly for older patients with severe dyskinesias who are at higher risk for adverse effects with STN DBS.

Patient selection for surgery

Patient selection aims at identifying those patients likely to benefit from surgery and unlikely to have severe adverse effects. Therefore, it is important to identify the disabling symptoms and assess if they are dopa-sensitive or dopa-induced and how they impact on the patient's daily life. A dopa challenge is very helpful to assess in detail 'off' symptoms, the response to medications and the severity and type of dyskinesias. Cognitive functions and mood should also be carefully assessed. Brain MRI is carried out to exclude contraindications such as severe atrophy, extensive white matter change and focal lesions. The patient's general condition has to be considered. Patients treated by platelet anti-aggregants or anticoagulants should be able to stop them for 2 weeks before and after surgery. Speech and swallowing have to be considered, because of the risk of deterioration. Patients and their family should be given detailed information about the procedure, its risks and potential benefits, as well as its limitations. Patient and family expectations have to be addressed. The choice of target depends on the profile of symptoms and the risk factors.

Surgery

Surgery is performed under stereotactic conditions. The implantation of the electrodes is usually carried out under local anesthesia. The target can be located using different imaging methods – brain MRI is now used for this by most surgeons. Brain atlases can also provide some guidance, in particular when the target cannot be visualized on MRI, e.g. the nuclei of the thalamus. During surgery different electrophysiological methods can be used. Microrecordings are used by many surgeons, although their safety is not entirely established. Intraoperative stimulation allows one to confirm the benefits and to observe side effects. The pacemaker and the connectors are usually implanted under general anaesthesia. The general risk of surgery includes haemorrhage in 1–4% of patients according to the technique and the surgeon, and infection of the system in about 2% of patients.

Stimulator adjustment and long-term management

Patients implanted with DBS need long-term follow-up by a specialist team. Stimulation parameters have to be adjusted from time to time, as well as medication. Electrical parameters are similar for all targets: voltage is usually between 2 and 4 V, pulse width usually 60 μs, occasionally 90 μs, but tends to be higher in GPi, and frequency is typically 130 Hz or above. Monopolar stimulation is preferred unless side effects limit the increase in voltage. Adjustment of thalamic DBS is usually straightforward. Adjustment of STN DBS has to be progressive, in parallel with adjustment of medications. Adjustment of GPi DBS does not have the same immediate effect on the symptoms. The pacemaker has to be changed approximately every 4–7 years.

Some side effects, in particular neuropsychiatric problems such as depression, apathy and mania, can occur a long time after surgery. Infections can also occur late and patients should take prophylactic antibiotics in appropriate circumstances. Some medical equipment, in particular diathermy and monopolar coagulation, should not be used in DBS patients. Brain MRI after implantation can only be performed under very restricted conditions of energy delivery and using a receiver–transmitter head coil.

The future

Existing DBS procedures, although very helpful, have limitations. They only allow symptomatic improvement, they do not appear to change the progression of the disease and they are ineffective against dopa-refractory symptoms, with the exception of tremor. There is no real alternative at present, although preliminary reports of DBS in the area of the pedunculo-pontine nucleus have suggested that it might improve gait.

Dopaminergic cell transplants and intraputaminal delivery of glial derived neurotrophic factor (GDNF) have shown apparent improvement in a minority of patients, but these procedures are currently halted while some of their side effects are investigated further. Further development of potentially disease-modifying and restorative procedures is the challenge for the future.

Dementia in association with Lewy body pathology

It has long been recognized that patients with PD have a higher risk of developing dementia than age-matched individuals who do not have PD. Cross-sectional studies gave average prevalence rates for dementia in the PD population of 15–30%, but this had to be an underestimate of the true cumulative risk because such subjects died sooner than those without dementia, leaving fewer prevalent cases. The first longitudinal study found a rate of 42%, and a recent study in Norway with 8-year follow-up gave a cumulative dementia risk of 78%. Cases with more than 1 year of parkinsonism before developing dementia are arbitrarily called Parkinson's disease dementia (PD-D).

Another clinical pattern is the development of parkinsonism and dementia within 1 year of each other, or a similar type of dementia without spontaneous parkinsonism but with the presence of Lewy body pathology (usually accompanied by varying numbers of senile plaques and sometimes of both senile plaques and neurofibrillary tangles) in both cerebral cortex and brainstem. This is called dementia with Lewy bodies (DLB), and is the most common cause of dementia in the elderly after Alzheimer's disease (AD; see Chapter 7). Mean survival of both DLB and PD-D cases after the development of dementia is only 5 years.

Progressive disabling mental impairment is a mandatory requirement for both PD-D and DLB. For probable DLB two, and for possible DLB one of three core features are required:

1 Fluctuating cognition with pronounced variations in attention and alertness;

2 Recurrent visual hallucinations; and

3 Spontaneous features of parkinsonism.

Features suggestive of DLB are REM sleep behaviour disorder, severe neuroleptic sensitivity and impaired dopamine transporter uptake in striatum on PET or SPECT scanning.

The management of confusion and hallucinations and of cognitive impairment in PD, PD-D and DLB is challenging. Intercurrent illness should be sought and treated. The number of different psychoactive (mostly antiparkinsonian) drugs taken should be reduced, starting with anticholinergics, then dopamine agonists and amantadine, then MAOB inhibitors, then catechol-*O*-methyltransferase (COMT) inhibitors, leaving the patient on monotherapy with a levodopa preparation in the lowest dose possible. If hallucinations or delusions persist, an antipsychotic drug may be needed. Risperidone and olanzapine are not recommended. Quetiapine is well tolerated, but not of proven efficacy in this indication. The only drug with class 1 evidence of antipsychotic efficacy, while not worsening underlying parkinsonism, is clozapine. However, because of the risk of bone marrow suppression and the consequent stringent monitoring requirements, it is little used in the UK in this indication, for which it is often considered a second-line drug.

The cortical cholinergic deficit in demented, and even in non-demented, PD patients and in DLB, is greater than that in AD. Therefore, the cholinesterase inhibitors are also effective in these indications. However, they may be more likely to worsen urinary frequency and urgency because of the underlying detrusor hyperexcitability in Lewy body diseases.

Multiple system atrophy

This sporadically occurring alpha-synucleinopathy was also previously described as Shy–Drager syndrome, striato-nigral degeneration, or (some cases) sporadic olivo-ponto-cerebellar atrophy (sOPCA). It causes varying combinations of parkinsonism (MSA-P, usually poorly responsive to levodopa), cerebellar dysfunction (MSA-C), autonomic failure (orthostatic hypotension, male erectile dysfunction and urinary incontinence or incomplete bladder emptying) and pyramidal signs. Pathology involves varying combinations and locations of neuronal loss and oligodendroglial pathology (ubiquitin and alpha-synuclein positive intracytoplasmic inclusions – GCIs) in striatum (especially posterior putamen), substantia nigra, locus caeruleus, inferior olives, pons and cerebellum, and in the intermediolateral cell columns and Onuf's nucleus of the spinal cord. Prevalence is about 4/100,000, mean age at onset is 57 years (never starting before age 30) and mean survival is about 7 (1–16) years. Often autonomic failure (AF) antedates the other neurology. If isolated AF persists for more than 5 years the term pure autonomic failure (PAF) is used – such patients usually have Lewy body pathology in autonomic ganglia, and also in nigra, but not enough to cause parkinsonism. Rare cases of MSA or of PD 'convert' from a label of PAF after the arbitrary 5-year period.

Other clinical features of MSA include RBD and sleep apnoea (also common, but less so, in PD), increased snoring, nocturnal or daytime stridor, emotional incontinence, myoclonic jerks of the fingers, impaired sweating and heat intolerance, Raynaud's phenomenon, cold dusky hands, disproportionate fixed antecollis, postural instability, dysphagia and a characteristic dysarthria – high-pitched, quivery, strained and hypophonic in MSA-P or slurring cerebellar-type in MSA-C. Frank dementia is rare, and an exclusion criterion for the diagnosis, because patients (usually more elderly) with the combination of dementia, parkinsonism and autonomic failure are much more likely to have Lewy body pathology. Consensus diagnostic criteria for MSA were recently revised (Gilman *et al.* 2008).

Progressive supranuclear palsy

Progressive supranuclear palsy (PSP) is a tauopathy, usually sporadic, rarely familial. It classically causes axial (hence symmetrical) akinesia and rigidity, early falls (classically backwards without warning), dysarthria (lower pitch, growling, with late groaning), dysphagia, personality change, frontal cognitive deficits and eye features. These include frontalis overactivity, levator inhibition, sometimes blepharospasm, and a characteristic supranuclear gaze palsy (or, more correctly, paresis) that is necessary for the clinical diagnosis and which gives the disease its name. Often the earliest feature is slowing of vertical voluntary saccades, followed by supranuclear limitation of up-gaze (non-specific) or down-gaze (always pathological), followed by similar abnormalities on horizontal saccades. The supranuclear cause of any limitation of voluntary gaze is identified when a complete range of automatic reflex eye movements is demonstrated by the oculocephalic, or doll's head, manoeuvre, such automatic–voluntary dissociation indicating that the oculomotor pathway from the nucleus distally is intact. The latency to initiate saccades is typically normal in PSP, in contrast to CBD (see below).

The pathology of PSP involves neuronal loss and gliosis, with straight neurofibrillary tangles and tufted astrocytes particularly in substantia nigra, dentate nucleus, pallidum, subthalamic nucleus and, to a variable degree, cerebral cortex.

The prevalence of PSP is about 5/100,000, mean age at onset is 63 years, never starting before 40, and mean survival is 7 years. Although about half of patients with pathologically proven PSP show the classic clinical picture (Richardson syndrome) with mean survival of 6 years, about one-third have a longer course averaging 9 years (PSP-P) with more PD-like features, including some levodopa response and resting tremor, with falls and gaze palsy developing later on. Other clinical features include emotional incontinence, frontal release signs, a memory retrieval deficit, palilalia and palilogia, other motor perseveration, sitting down 'en bloc' and prominent sialorrhoea. Despite severe postural instability, patients usually fail to widen their base which, combined with 'motor recklessness', causes frequent falls, with injury. Unlike MSA and PD, cardiovascular AF is not a feature of PSP. However, urinary disturbance is common. Currently used research diagnostic criteria are those of Litvan *et al.* (1996).

Cortico-basal degeneration

This tauopathy is also largely sporadic, with only very rare familial cases. Nevertheless, it shares with PSP over-representation of the H1/H1 tau haplotype, indicating some shared genetic susceptibility. Those with the disease classically present to movement disorder specialists with the asymmetric and progressive evolution, usually starting in one arm (but sometimes in a leg), of 'difficulty' using the limb, which progressively becomes useless because of a combination of akinesia, rigidity, fixed dystonia, myoclonus, jerky tremor, cortical sensory loss and, above all, apraxia. Sometimes there is an additional 'alien limb' phenomenon, when the limb wanders off 'with a mind of its own'. Progression is then to the opposite limb or the other limb on the same side, ultimately to all four limbs, and a supranuclear gaze palsy (paresis) gradually develops which classically is the 'mirror-image' of PSP. Thus, there is great difficulty initiating voluntary saccades, with prolonged latency, but when the eyes finally move they do so with normal velocity. The pathology of CBD involves swollen ('ballooned') cortical neurones predominantly in frontal and parietal areas.

The prevalence of CBD is unknown, but it is rarer than MSA or PSP. Mean age at onset is 63 years and mean survival is 8 years.

The classic clinical picture described above can be misleading. Thus, those with CBD may present to dementia specialists with apraxia or primary progressive aphasia, or disease may present symmetrically, or with falls. Other diseases can also present with a cortico-basal-like syndrome, including strokes and prion disease.

Ancillary investigations to distinguish between PD, MSA, PSP and CBD

MRI of brain in MSA may reveal, supratentorially, putaminal atrophy, a hyperintense slit-like lateral rim to the putamen, or posterior putaminal hypointensity (Plate 5.1). Infratentorially, pontine atrophy, a 'hot-cross bun' appearance of the pons in cross-section, hyperintensity of the middle cerebellar peduncles, or cerebellar atrophy may be seen.

In PSP one may see atrophy of the midbrain, as evidenced by the 'hummingbird sign' on sagittal cuts, and atrophy of the superior cerebellar peduncles on axial cuts (best demonstrated with voxel-based morphometry). In CBD there may be asymmetrical or unilateral frontal and parietal atrophy.

F-dopa PET (FDG PET) or dopamine transporter SPECT scans only provide evidence of nigral pathology, so cannot reliably distinguish between these conditions. However, a normal scan can provide useful evidence in favour of psychogenic or drug-induced parkinsonism, or of essential or dystonic tremor, or in distinguishing between dopa-responsive dystonia (normal) and 'juvenile PD' (abnormal). FDG-PET may show a signal void in striatum in MSA (and PSP), and asymmetrical fronto-parietal hypometabolism in CBD. Cardiac ^{123}I meta-iodobenzyl guanidine (MIBG) scanning usually, but not always, reveals evidence of post-ganglionic cardiac denervation in PD, whereas such scans are typically, but again not always, normal in MSA, PSP and CBD.

Autonomic function tests can reveal evidence of autonomic failure, but not whether it is caused by Lewy body pathology or MSA.

Urethral or anal sphincter elctomyography (EMG) can show evidence of denervation and reinnervation (increased amplitude, duration and polyphasia) consequent on loss of anterior horn cells in Onuf's nucleus at S2–3. A normal result would argue against MSA, but abnormal results occur also in PD and PSP. The growth hormone response to clonidine infusion is abnormal in MSA, and in some patients with PD; the response to an arginine infusion may be a better discriminator.

Vascular parkinsonism

Subjects with multiple infarcts or, more commonly, multiple basal ganglia lacunes or deep white matter vascular changes, can present with what is often a poor mimic of PD or even of true parkinsonism. Typically, spontaneous movements and facial expression are good, posture upright, and while there may be pyramidal slowing of finger movements, there is no classic fatiguing or decrement, and no tremor. The gait may be wide-based or unsteady, and small-stepped (*marche à petits pas*) rather than shuffling. Start hesitation or gait initiation failure, freezing and some fatiguing of alternating ankle movements are often present, leading to terms such as lower body parkinsonism or parkinsonian ataxia. True parkinsonism involving upper as well as lower body, in the presence of cerebrovascular disease (CVD) is usually brought about by the co-occurrence of PD – the patient's upper body has levodopa-responsive parkinsonism while their lower half behaves differently, and gait problems and falls often appear or worsen suddenly or subacutely. However, some cases of apparent true parkinsonism resulting from CVD, with no Lewy body pathology, have been reported, and some of these have responded to levodopa, so that a trial of this drug is probably justified in all cases of CVD with 'parkinsonian' features.

Ethnic or region-specific parkinsonism

X-linked dystonia-parkinsonism ('Lubag') with striatal mosaicism is essentially limited to Filipinos. The parkinsonism–dementia–ALS complex in Guam, a disease characterized by tangle pathology rather than Lewy bodies, may be of environmental, rather than genetic, origin, as it is fast disappearing. Atypical parkinsonism on Guadeloupe may be heterogenous, and at least partly environmentally determined.

Other causes of parkinsonism

Other genetic causes include the Huntington's disease Westphal phenotype, mostly in juvenile onset cases; Wilson's disease; SCAs 1–3, in which tremor and levodopa-responsiveness may be seen; FTDP-17; and other rarer causes (Table 5.2).

Environmental causes include toxins (MPTP, CO, methanol and manganese) and drugs (dopamine receptor blockers, presynaptic dopamine depletors); post-infectious, particularly after Japanese B encephalitis and encephalitis lethargica (which still occurs rarely, with positive antibasal ganglia antibodies): post-traumatic, in boxers with punch drunk syndrome; hydrocephalus and tumour.

Tremor

Tremor is defined as rhythmic sinuisoidal alternating movement. It can be described in several ways: e.g. rest; postural; action or terminal; or intention. Tremor in PD, MSA and PSP has been discussed above.

Benign essential tremor

This is commonly inherited as an autosomal dominant trait. Most people with essential tremor (ET) have little or no disability, so never see a neurologist. Published community prevalence figures vary hugely, but an average of studies is 3–400/100,000. Typically, ET involves both arms first, fairly symmetrically, and to a greater degree than any other body parts (neck, legs, voice) which may be subsequently involved. The tremor is usually vertical (flexion–extension) rather than pronation–supination. It often worsens slowly over many years, but even then often does not cause marked functional impairment, although in some cases it does. It often improves after alcohol, and may be helped by β-blockers, primidone, gabapentin and topiramate in some cases.

Dystonic tremor

The authors' view of dystonic tremor is that it is poorly defined, under-recognized and often misdiagnosed as ET or as benign tremulous PD. This Queen Square view is controversial, and not yet generally accepted. The Movement Disorder Society Consensus Statement on Tremor restricts the term dystonic tremor to a tremor in a body part also displaying overt dystonia (e.g. tremulous torticollis). When someone with spasmodic torticollis, for example, also has a tremor of one or both arms, without overt dystonia in those limbs it is called tremor associated with dystonia. Such an arm tremor usually displays other characteristics: it may be unilateral or asymmetrical, relatively slow ('myorhythmia'), pronation–supination, coming in 'flurries', jerky, position-specific or markedly worsened by certain tasks (e.g. attempting to write), and therefore more commonly disabling than ET; it can be associated with abnormal or reduced arm swing, or a jaw tremor, and about one-third of these patients also display a dominant family history (in taking a family history of tremor it is always useful to ask what shook [e.g. neck] as well as who shook). We would also call this tremor dystonic tremor. Where the patient has tremor with these characteristics, but (as yet) no evident dystonia, we currently label this as atypical tremor, whilst recognising that many of these subjects may later turn out to have dystonic tremor. Drug treatment is disappointing in older patients, but levodopa and anticholinergics are worth trying in younger subjects.

Both ET and dystonic tremor can be helped by botulinum toxin injections or, in severe cases, thalamic DBS or pallidal DBS (if dystonic).

Neuropathic tremor

Some neuropathies, particularly IgM dysgammaglobulinaemic neuropathy, can cause a postural (and if severe, even a resting) tremor. The severity of the tremor does not necessarily correlate with the severity of the neuropathy or the degree of deafferentation. In patients with unexplained tremor it is always important to search for any clinical evidence of neuropathy.

Fragile X tremor ataxia syndrome (FXTAS)

It has recently been recognized that individuals (usually males) with premutations (55–200 CGG repeats) in the fragile X mental retardation 1 (*FMR1*) gene may, as they get older, present with a relatively slowly (compared to MSA-C) progressive syndrome combining postural or action tremor and ataxia, sometimes with additional parkinsonism, peripheral neuropathy, cognitive impairment and dysautonomia. There may be a family history of, and an increased risk, especially to males, of mental retardation, and premature ovarian failure may occur in females. MRI commonly shows hyperintensity of the middle cerebellar peduncles or of subcortical white matter, and cerebellar atrophy.

Cerebellar (pathway) tremor

Intention tremor

This is caused by brainstem or cerebellar outflow pathway lesions, the most common cause being multiple sclerosis. The tremor is not just action or terminal (features common to many postural tremors), but worsens steadily throughout the whole trajectory of the movement. Symptomatic drug treatment is unhelpful. DBS may transiently help, but its benefits are usually overwhelmed by the progression of lesion load.

Holmes tremor

This form of tremor, previously called midbrain tremor or rubral tremor, is a tripartite tremor incorporating tremor at rest, postural tremor and intention tremor. It is caused by a combination of damage to the cerebello-rubrothalamic and nigro-striatal pathways.

Palatal tremor

This comprises rhythmic (1–2 Hz) contractions of the soft palate, presumably resulting from a dysfunction (essential palatal myoclonus [EPM]) or a lesion (symptomatic palatal myoclonus [SPM]) involving the connections between dentate nucleus, red nucleus and inferior olivary nuclei (the Guillain–Mollaret triangle). EPM consists of rhythmic contractions of the tensor veli palatini, innervated by the trigeminal nucleus; in SPM, the main muscle involved is the levator palatini, innervated by the facial nucleus and the nucleus ambiguus. EPM is typically associated with clicking, whereas SPM usually persists during sleep and is often associated with hypertrophy of the inferior olive. SPM is often associated with vertical ocular movements (oculopalatal myoclonus) or rhythmic and oscillatory limb movements at a rate of 1–3 Hz. Important causes of SPM include Wilson's disease, stroke and/or tumour and Alexander's disease. Oculomasticatory myorhythmia or oculo-facial-skeletal myorhythmia are said to be pathognomonic of Whipple's disease. Clonazepam sometimes helps.

Orthostatic tremor

This is a rare condition in which subjects feel unsteady, and often tremulous, while standing still, but not on walking, so that they like to either sit down or to keep moving (the 'white rabbit syndrome'). It is characterized by 16 Hz tremor of the leg muscles, easily recorded on surface EMG which can often be felt or auscultated, but not usually seen. Some cases have additional features of parkinsonism or restless legs. Clonazepam sometimes helps.

Drug and toxin-induced tremor

Tremor can be caused by a number of different drugs or toxins including dopamine-depleting or receptor-blocking drugs, cinnarazine, some calcium-channel blockers, e.g. diltiazem (mostly rest tremor), sodium valproate (rest or postural), or beta-agonists, theophylline, caffeine, nicotine, lithium, amiodarone, SSRIs and tricyclic antidepressants, ciclosporin, thyroxine excess, and intoxication with marijuana, cocaine, amphetamines or mercury (postural).

Psychogenic tremor

This is dealt with under other movement disorders.

Dystonia

Dystonia is a heterogeneous and common movement disorder typically characterized by involuntary muscle spasms leading to abnormal postures of the affected body part. Typically, the spasms in dystonia are mobile and this often leads to a slow writhing of the affected body part as described by the older term 'athetosis'. Co-contraction of agonist and antagonist muscles is the underlying reason for the abnormal posturing in dystonia, and this can be obvious clinically or more easily on simple EMG assessment. Dystonia can be variable in its presentation and in some cases tremor or jerks may be the predominant feature with the abnormal postures being subtle. Dystonia can also often be task, or position-specific, e.g. present only on writing or playing a musical instrument but not with other tasks. Another characteristic feature of dystonia, particularly focal dystonia, is the presence of a sensory trick or 'geste antagoniste', whereby applying a sensory stimulus to a particular area will cause the abnormal posture to resolve.

Epidemiology

There have been few epidemiological studies of dystonia. Most studies have provided estimates based on few cases. A European prevalence study with pooled data from eight countries undertaken to provide more precise rates of dystonia found the crude annual period prevalence rate (1996–1997) for all primary dystonia was 152 per million, with focal dystonia having the highest rate of 117 per million (108–126) of which cervical dystonia was most common (57 per million), followed by blepharospasm (36 per million) and writer's cramp (14 per million). However, the authors pointed out that because of under-ascertainment of cases, these rates were probably an underestimate of the true prevalence of dystonia.

Classifying dystonia

Dystonia can be classified in a number of ways including by age of onset, by distribution and aetiology (Table 5.3). With regard to aetiology there have been major advances in the genetic causes of the dystonias and this list keeps growing. Clinically, however, the most important and useful division is classifying patients broadly into two categories: those with 'primary dystonia'; and those with 'secondary/heredodegenerative' dystonic conditions. Dystonia is the only clinical sign (with the exception of tremor) in primary dystonia, and there is no neurodegeneration. The age of onset (below or above age 28), and distribution (focal, segmental, generalized) can be very useful to decide whether the patient fits into the well-defined phenotypes of primary dystonia (see below), and for picking up patients with unusual phenotypes (e.g. an adult presenting with generalized dystonia, which would be incompatible with typical primary dystonia) and to investigate these patients further to find out the likely secondary/heredodegenerative cause. Clinical features or 'red flags' that should make one consider secondary dystonia rather than primary dystonia are listed in Table 5.4.

Psychogenic dystonia is dealt with later in this chapter (see Other movement disorders).

Primary dystonia

In patients with primary dystonia, age at onset appears to be very important in determining the clinical phenotype. Young onset dystonia (before the age of 28 years) most commonly manifests with limb onset dystonia, followed by subsequent generalization and was referred to in the older literature as dystonia musculorum deformans or Oppenheim's dystonia. It is now known that about 70% of patients presenting in this way will carry a single GAG deletion in the *DYT1* gene on chromosome 9. This condition is more common in Ashkenazi Jews, with a possible founder in Eastern Europe about 3 centuries ago. It has an autosomal dominant inheritance, but a very low phenotypic penetrance such that only 30–40% of gene carriers will ever develop dystonia, and in those who do this will almost always happen before the age of 30 years.

When dystonia appears in adult life, a focal or segmental distribution is commonly seen and the condition does not generalize. These presentations, in order of frequency of occurrence, include cervical dystonia (spasmodic torticollis), cranial dystonia (e.g. blepharospasm, Meige syndrome [blepharospasm and oromandibular dystonia]), writer's cramp, laryngeal dystonia (sometimes called spasmodic or, inappropriately, spastic dysphonia) and other task-specific dystonias. Cranio-cervical dystonia is more common in women than men, with the opposite pattern seen in task-specific writing dystonia. The adult onset focal dystonias are not a forme fruste of the early onset *DYT1* gene-related dystonia, and this gene has been excluded in these disorders, most of the patients being sporadic. However, three genetic loci

Table 5.3 Classification of dystonia.

By aetiology	By distribution	By age at onset
Primary (no neurodegeneration; dystonia only +/– tremor)	Focal	Young onset (<28 yrs)
	Segmental	Adult onset (>28 yrs)
Dystonia-plus syndromes	Multifocal	
Dopa-responsive dystonia	Hemidystonia	
Myoclonus dystonia		
Secondary		
Symptomatic		
Heredodegenerative		
Paroxysmal		

Table 5.4 Clinical clues in the history and examination suggesting a secondary cause of dystonia.

- Abnormal birth/perinatal history
- Developmental delay
- Continued progression of symptoms
- Unusual distribution of dystonia given age of onset (e.g. leg dystonia in an adult, hemidystonia)
- Unusual nature of dystonia (e.g. fixed dystonic postures)
- Prominent bulbar involvement by dystonia
- Additional neurological symptoms (pyramidal signs, cerebellar signs, cognitive decline)
- Seizures
- Other systems affected (e.g. organomegaly)
- Previous exposure to drugs, e.g. dopamine receptor blockers

Table 5.5 A list of the dystonia genetic conditions.

Name	Gene	Mode of inheritance	Clinical features
DYT1	*DYT1*	AD	Young onset primary generalized dystonia
DYT2	n.k.	AR	Recessive young onset primary dystonia in a single Spanish gypsy family
DYT3	Linkage to X13.1	XR	Dystonia parkinsonism in Filipino males
DYT4	n.k.	AD	Laryngeal dystonia (whispering dysphonia) +/– limb dystonia in a single Australian family
DYT5 (DRD)	*GTPCH1*	AD	Young onset dopa-responsive dystonia/parkinsonism
DYT6	Linkage to 8p21-p22	AD	Two Mennonite families with variable onset of primary craniocervical and limb dystonia
DYT7	Linkage to 18p	AD	Single(?) German family with primary craniocervical dystonia
DYT8 (PNKD)	*MR-1*	AD	Attacks of dystonia and chorea precipitated by coffee, alcohol and fatigue
DYT9	Linkage to 1p	AD	Episodic chorea and ataxia with progressive interictal spasticity
DYT10 (PKD)	Linkage to centromeric region of chromosome 16	AD	Episodes of chorea and dystonia precipitated by sudden movement
DYT11	ε-sarcoglycan gene	AD	Myoclonus and dystonia
DYT12	*ATP1A3*	AD	Rapid onset dystonia following infection/exercise
DYT13	Linkage to 1p36.13	AD	Single Italian family with primary cranio-cervical dystonia
DYT14	Linkage to 14q13 outside region for *GTPCH1* gene	n.k.	Dopa-responsive dystonia parkinsonism

AD, autosomal dominant; AR, autosomal recessive; XR, X-linked; n.k., not known; DRD, dopa-responsive dystonia; PKD, paroxysmal non-kinesigenic dyskinesias; PNKD, paroxysmal non-kinesigenic dyskinesias.

– *DYT6*, *DYT7* and *DYT13* – have been described in rare families with cranio-cervical segmental dystonia but the genes are yet to be discovered (Table 5.5) and the disorder is likely to be even more genetically heterogenous, as a number of autosomal dominant craniocervical dystonia families do not link to these three loci.

Dystonia-plus syndromes

This category refers to two diseases without evidence of neurodegeneration whose motor manifestations are restricted to dystonia, plus parkinsonism or myoclonus. Some would consider it reasonable to include them with *DYT1* under the heading of primary dystonias.

Dopa-responsive dystonia

Dopa-responsive dystonia (DRD; *DYT5*), previously also called Segawa disease, typically presents in childhood, purely with lower limb dystonia, and parkinsonism may rarely be associated, although the latter can be a presenting feature when onset is at an older age. A diurnal fluctuation in symptom severity with a gradual worsening of symptoms throughout the day was said to be typical of the condition, but is present in only 60% of cases. This condition is inherited in an autosomal dominant manner, with reduced penetrance, and is caused by mutations in the GTP cyclohydrolase 1 gene (*GTPCH1*; *DYT5*), a rate limiting step in the production of dopamine from tyrosine. Although rare, it is of critical importance to the practising neurologist as it is entirely treatable by small doses of levodopa. This typically leads to complete resolution of symptoms which is sustained, without the development of long-term complications as seen in PD.

It is increasingly recognized that DRD can present with unusual phenotypes such as spastic diplegia, writer's cramp and other focal dystonias including predominant cervical dystonia and even ataxia. In view of this, an adequate trial of levodopa (ideally up to 100–200 mg plus peripheral decarboxylase inhibitor t.d.s., according to age, for at least 2 months) is strongly recommended in all those with young onset dystonia, especially as genetic diagnosis is time-consuming and not generally available. A phenylalanine loading test and cerebrospinal fluid (CSF) pterin studies may be helpful. It is also important to differentiate patients with DRD from those with young onset Parkinson's disease, who may present with foot dystonia, and in whom the early use of levodopa is not recommended. A DaT SPECT or a fluorodopa PET scan (both normal in DRD) can be useful in this regard. Other inherited defects of the dopamine synthesis pathway, e.g. the recessively inherited tyrosine hydroxylase deficiency, can also cause DRD, but usually as part of a more severe neurological syndrome.

Myoclonus dystonia

Patients with myoclonus-dystonia (*DYT11*), caused by autosomal dominantly inherited mutations in the ε-sarcoglycan gene on chromosome 7q21, present with early onset dystonia in combination with myoclonic 'lightning' jerks. The jerks respond quite dramatically to alcohol. The condition typically starts in childhood, and is mostly inherited through the father because of maternal genomic imprinting. The myoclonus or dystonia mainly affects the head, neck and arms, with the legs usually being spared. The myoclonus worsens during movement (action myoclonus) and is often more prominent than the dystonia. It had been suspected that hereditary essential myoclonus (when myoclonus is prominent) and dominantly inherited myoclonic dystonia, with lightning jerks and dramatic response to alcohol, might often be the same disease, and this has now been confirmed with the discovery of the causative mutations, although other broadly similar cases are mutation-negative. Psychiatric features such as anxiety, depression and obsessive-compulsive disorders are also a feature of the condition in a proportion of cases.

Symptomatic dystonia

Dystonia can be secondary to a number of environmental causes, many of which affect the basal ganglia. Dystonia is commonly seen following brain injury, e.g. perinatally (dystonic/dyskinetic/athetoid cerebral palsy) or following stroke. In such patients a static deficit is commonly seen, although onset can be delayed for months or even years after injury, and progression and late worsening of symptoms is sometimes seen.

Tardive dystonia is dealt with under Other movement disorders, below.

Heredodegenerative dystonias

Dystonia can be a feature of a wide range of neurodegenerative conditions, which can make selection and prioritization of the appropriate investigations and reaching the correct diagnosis a difficult task. One aspect of such conditions that can be helpful is that many have syndromic associations which can help guide the investigating clinician. For example, peripheral neuropathy in association with dystonia would make one think of neuro-acanthocytosis or metachromatic leuco-dystrophy as more likely diagnoses. Prominent facial dystonia or flapping tremor would make one consider Wilson's disease and associated ataxia may point to spino-cerebellar degenerations such as SCA2 or SCA3. Prominent bulbar or severe tongue involvement by dystonia is a strong pointer to secondary dystonia and would favour certain conditions including neurodegeneration with brain iron accumulation (NBIA; formerly known as Hallervorden–Spatz syndrome) and also neuro-acanthocytosis and Lesch–Nyhan syndrome. Appropriate investigation should be carried out. Brain MRI is very important as it may show characteristic changes, e.g. the 'eye of the tiger sign' characteristic of NBIA caused by mutations of the pantothenate kinase 2 gene (*PANK2*) (Figure 5.1). A list of some of these conditions, with their associated clinical symptoms, is given in Table 5.6, and the investigations to be carried out as suggested by the syndromic association are given in Table 5.7.

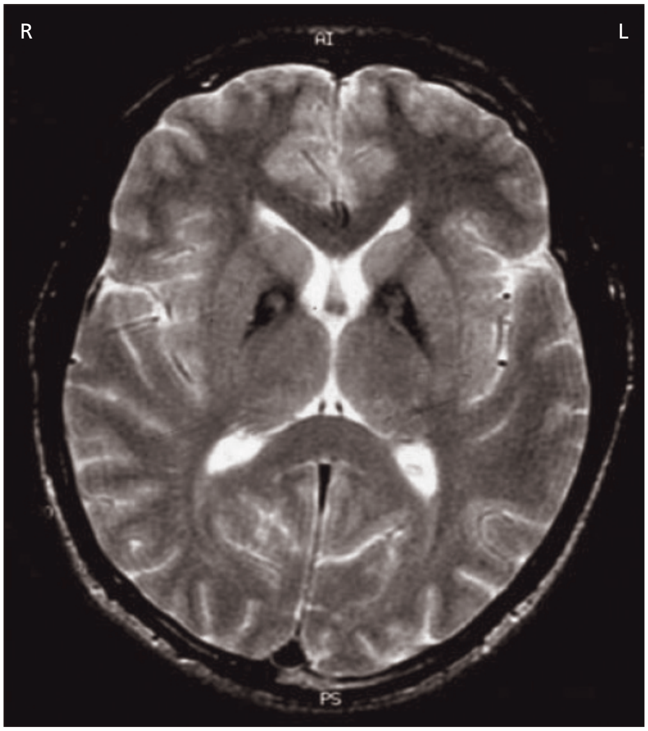

Figure 5.1 Classic 'eye of the tiger sign' (central hyperintensity with surrounding hypointensity in globus pallidus) in a patient with neurodegeneration with brain iron accumulation (NBIA) caused by a *PANK2* mutation (MRI T2W).

Table 5.6 Examples of common heredodegenerative causes of dystonia and associated syndromic clinical features.

Wilson's disease	Kayser–Fleischer rings, ataxia, cognitive decline
Neurodegeneration with brain iron accumulation (PANK2, Hallervorden–Spatz syndrome)	Retinal degeneration, pyramidal signs, oromandibular/bulbar involvement
Neuro-acanthocytosis	Peripheral neuropathy, oromandibular dystonia, epilepsy
Metachromatic leuco-dystrophy	Peripheral neuropathy, frontal dementia
GM1/GM2 gangliosidosis	Cognitive decline
Glutaric acidemia	Cognitive decline
Huntington's disease	Cognitive decline, personality change, depression, supranuclear eye movement abnormalities
Ataxia telangiectasia	Supranuclear eye movement abnormalities
Niemann–Pick Type C	Vertical gaze palsy, cognitive decline

Table 5.7 List of investigations in those suspected of secondary dystonia depending on syndromic associations in Table 5.6.

MRI brain/spine (structural lesions, leuco-dystrophies, 'eye of tiger' sign in NBIA)
Nerve conduction studies (neuro-acanthocytosis, metachromatic leuco-dystrophy)
Copper studies, slit-lamp, ?liver biopsy (Wilson's disease)
White cell enzymes (GM1, GM2, metachromatic leuco-dystrophy)
Alphafetoprotein, immunoglobulins (ataxia telangiectasia)
Lactate/pyruvate, mitochondrial mutations, muscle biopsy (mitochondrial disease)
Fresh thick blood smear for acanthocytes (neuro-acanthocytosis)
Plasma amino acids, urinary organic acids, aminoacids, oligosaccharides (glutaric academia, GM1, GM2)
Bone marrow biopsy/axillary skin biopsy (Niemann–Pick Type C, Kufs)
Phenylalanine loading test/CSF pterin assessments (DRD)
ERG, retinal examination, PANK2 gene test (positive in some cases of NBIA)
Huntington's disease gene test

DRD, dopa-responsive dystonia; ERG, electroretinogram; MRI, magnetic resonance imaging; NBIA, neurodegeneration with brain iron accumulation.

Wilson's disease

Of all the causes of heredodegenerative dystonia, Wilson's disease (WD) is the most important because it is treatable, but fatal if left untreated. It is an autosomal recessive disorder of copper metabolism that most commonly presents in the first two decades of life. It occurs worldwide with prevalence of 1–3/100,000. More than 300 different mutations have been identified distributed across the responsible gene, *ATP7B* on chromosome 13, which encodes a copper-dependent transmembrane protein P type ATPase. The most common in patients of European origin is the H1069Q mutation. The heterozygote carrier rate is 1%.

Clinical presentations

Patients may present with acute liver failure, chronic hepatitis or cirrhosis, most commonly in the first decade of life, and a few present with an acute haemolytic anaemia. Other features include joint and bone abnormalities, azure lunulae of the finger nails, aminoaciduria and cardiomyopathy.

Most cases of neurological WD present with slurred speech and a movement disorder in adolescence, often in association with behavioural disturbances. Approximately half of all cases present with neuropsychiatric symptoms, usually between 14 and 20 years of age.

The 'pseudosclerotic' neurological variant is perhaps the most common, with the onset of a Holmes or wing-beating tremor and some ataxia and dysarthria; in other patients dystonia or an akinetic-rigid syndrome may dominate. Early gait abnormalities are frequent and a mixed movement disorder is common, sometimes with associated risus sardonicus and pseudobulbar palsy. Dysarthria is the most common sign, whereas chorea and athetosis affect only about 10%. If left untreated, fronto-limbic cognitive dysfunction may develop and seizures, myoclonus and pyramidal signs have been reported. Cases presenting later than age 40 are exceptionally rare. Virtually every patient with WD presenting with neurological dysfunction has Kayser–Fleischer (K-F) rings on slit-lamp examination. These are caused by copper deposition on the inner surface of the cornea in Descemet's membrane and have a golden brown or greenish appearance. They can occur in other forms of chronic liver disease but in the context of a neurological presentation in adolescence can be considered pathognomonic for WD.

The histopathological findings in the brain include swollen glia and an increase in astrocytes within the grey matter, often with spongiform change.

Diagnosis

The emergence of parkinsonism, dystonia or a tremor in an adolescent or young adult with slurred speech should always raise the possibility of WD, particularly if there is a family history of hepatic, psychiatric or neurological disorder in childhood. Consanguinity should be enquired about. Suspected cases should be referred to an experienced ophthalmologist for slit-lamp examination.

The combination of a movement disorder with emotionalism, a risus sardonicus and a K-F ring makes the diagnosis highly likely but biochemical confirmation is required. Unfortunately, there is still no one single failsafe test.

A low serum caeruloplasmin level is consistent with WD and is diagnostic when K-F rings are present. Low levels of caeruloplasmin also occur in hereditary acaeruloplasminaemia and Menkes disease. Some WD heterozygotes have a reduced caeruloplasmin level, while a few WD patients with decompensated liver disease may have normal levels. In females, the oral contraceptive pill may raise an otherwise low level to within the normal range. In WD, a hepatic copper concentration greater than 250 μmg/gm dry weight is usual. Serum aminotransferase levels are also usually abnormal. However, a lower hepatic copper value does not absolutely exclude WD and long-standing cholestasis may also cause high copper levels. The biochemical results therefore need to be taken in the context of the clinical picture and the histological changes. Although genetic testing is not available as a routine service test, in ambiguous cases it may be extremely helpful to at least screen for the more common mutations. Urinary copper, derived from the free non-caeruloplasmin-bound copper circulating in plasma, is elevated in WD. An excretion rate greater than 100 μg/24 hours (0.6 mmol/L in 24 hours) is considered diagnostic but levels above 40 μg/24 hours may be significant in a neurological presentation. Wide-necked bottles with copper-free disposable polyethylene liners are recommended. Urinary copper excretion after penicillamine loading can be a useful ancillary test.

In neurological cases, brain MRI may show high signal abnormalities on T2 weighted images and low intensity lesions on T1 in the putamen, globus pallidus, thalamus, midbrain, pons and cerebellum. White matter abnormalities are also common and cortical atrophic changes may also occur. Proton density MRI sequences may be particularly sensitive. Once WD has been diagnosed, screening of all first degree relatives is essential.

Treatment

The first chelation treatment, parenterally administered British anti-Lewisite (BAL), was introduced in 1951. In 1956, John Walshe first reported clinical benefit with penicillamine and half a century of use has confirmed its efficacy in most cases. However, some patients cannot tolerate the drug and about 20% of patients with neurological presentations may deteriorate markedly on its introduction. Regular monitoring with a full blood count and renal function tests is recommended. Adverse events include fever, rash, lymph gland enlargement, neutropenia, thrombocytopenia and proteinuria. Nephrotoxicity, a lupus syndrome, bone marrow suppression, skin changes including elastosis perforans serpiginosa and a myaesthenic syndrome are late complications. Children and pregnant women should be given weekly pyridoxine.

In 1969, Walshe discovered another chelator, trientene, which has proved to be a well-tolerated alternative. It is still generally used as a second line drug, but some now recommend it as the initial treatment of choice in neurological cases, although deterioration can also occur on starting treatment. Pancytopenia has been reported and sideroblastic anaemia may occur if copper deficiency develops.

Oral elemental zinc, which induces intestinal metallothionein which binds copper within the enterocyte, has also been recommended, particularly for asymptomatic and presymptomatic patients and as maintenance therapy after a period of initial chelation.

Tetrathiomolybdate forms a complex with copper and protein and prevents copper absorption when given with food, and has been claimed to be highly effective, but remains investigational. Whichever drug is chosen, regular lifelong monitoring to ensure compliance is essential.

Chocolate, liver, nuts, mushrooms and shellfish contain high levels of copper, so are best avoided. Anticholinergics may modestly help dystonia and some patients with an akinetic-rigid syndrome may have some improvement with levodopa. In patients with hepatic disease who deteriorate despite optimum therapy, liver transplantation, which corrects the underlying pathophysiology, can be life-saving. For refractory or deteriorating neurological disability despite other treatments, a course of intramuscular BAL injections is worth trying. The use of liver transplantation for patients with progressive neurological impairment despite adequate chelation is controversial. Patients with WD surviving into middle age have an elevated risk of hepatic carcinoma.

Paroxysmal dyskinesias

Paroxysmal dyskinesias are defined as intermittent attacks of involuntary movements, usually dystonia, chorea or ballism, with normal neurological examination between attacks. Episodes are induced by trigger factors including sudden movements (paroxysmal kinesigenic dyskinesia [PKD]), prolonged exercise (paroxysmal exercise-induced dyskinesia [PED]) or alcohol and coffee (paroxysmal non-kinesigenic dyskinesia [PNKD]) or sleep (paroxysmal nocturnal dyskinesia [PND]). The duration can be seconds to hours. Recently, mutations in the myofibrillogenesis regulator gene (*MR-1*) on chromosome 2q33–35 have been identified in patients with PNKD. The encoded protein appears to have a role in the detoxification pathway of methylglyoxal, a compound present in coffee and alcoholic beverages, both of which can induce attacks. In PND, nicotinic acetylcholine receptor gene mutations occur and this is an example of a ligand-gated channelopathy. For the other forms, various loci have been proposed but genes have not yet been identified. Secondary paroxysmal dyskinesias have also been described and possible causes include demyelination, vasculopathy, infectious disease (HIV, cytomegalovirus), cerebral and peripheral trauma, neurodegenerative disease, hormonal and metabolic dysfunction, neoplasm and cerebral palsy. Anticonvulsants (first choice carbamazepine), benzodiazepines, barbiturates or acetazolamide can bring relief. Triggering factors should be avoided.

Investigation of dystonia

Following a careful history (in particular drug and family history) and examination, investigation of patients with dystonia should be tailored to the presentation of the patient, and in particular whether the clinical picture suggests primary or secondary dystonia. Common clinical situations are of children or adolescents presenting with a primary focal, segmental or generalized dystonia, or adults presenting with a primary focal or segmental dystonia. For the former category, investigations should include copper studies and slit-lamp to exclude WD, brain imaging (preferably MRI), the *DYT1* gene test and an adequate trial of levodopa. For adult onset primary dystonia, copper studies and slit-lamp to exclude WD may be performed if presentation is under 50 years of age; brain imaging is not generally required, but if there is fixed or painful cervical dystonia an MRI of the spine should be carried out to exclude structural lesions. More extensive investigations are needed in patients with presumed secondary dystonias (Table 5.4) but this list can be narrowed down by considering pertinent aetiological possibilities according to the presence of associated clinical features as shown in Table 5.6, and an outline of the investigations is given in Table 5.7.

Treatment of dystonia

Drug treatment of dystonia is most appropriate in those with younger onset generalized and/or segmental dystonia for whom botulinum toxin (see below) would be unlikely to control the full extent of the dystonia. First line treatment is with anticholinergics such as trihexyphenidyl. Slow introduction of the drug is very important to avoid side effects, but some, particularly younger, patients can ultimately tolerate very high doses (100 mg/day or more) with good effect. Clonazepam can be useful for the treatment of tremor, jerks and pain associated with dystonia. Other drugs that are sometimes useful include tetrabenazine, baclofen and even dopamine receptor blocking drugs. As mentioned above, all patients with young onset dystonia should receive an adequate trial of levodopa. The treatment of WD has been detailed above.

Botulinum toxin has revolutionized the treatment of patients with focal dystonia. Botulinum toxin cleaves specific proteins involved in vesicular fusion at the presynaptic terminal, thereby blocking the release of acetylcholine, the principal neurotransmitter at the neuromuscular junction. The affected nerve terminals do not degenerate, but the blockage of acetylcholine release is irreversible. Neuromuscular transmitter release recovers by sprouting of new nerve terminals and formation of new synaptic contacts, which takes about 3 months. Transmission is also inhibited at gamma neurones in muscle spindles, which may alter reflex overactivity.

A number of randomized double-blind clinical trials have established the efficacy of botulinum toxin injection treatment for focal dystonia. Treatment is required every 3–4 months, and is expensive, but a 70–80% improvement in symptoms is common in most patients, particularly those with blepharospasm and cervical dystonia. Treatment of those with limb dystonia, in particular writer's cramp, is often more difficult and benefit can be inconsistent. Main side effects of treatment are excessive weakness of the treated muscle or spread of effect to nearby muscles (e.g. paralysis of pharyngeal muscles following sternomastoid injections). Immune-mediated resistance to botulinum toxin is seen in a small proportion of chronically treated patients, particularly those who receive high doses, 'top-up' doses or injections more frequently than every 12 weeks. An alternative toxin, botulinum toxin type B, is available, but antibodies to the commonly used type A toxin can be cross-reactive with type B toxin, and, in addition, a primary immune response to type B toxin can also occur. Botulinum toxin can be helpful for those with generalized dystonia where a particular functional problem can be linked to dystonia in a single or a small group of muscles.

Surgery for dystonia

Although the primary treatment for dystonia is medical, a number of patients, particularly those with generalized dystonia, remain severely disabled and may benefit from surgery. Ventrolateral thalamotomies, and to a lesser degree pallidotomies, were performed from the 1950s for alleviation of dystonia. The results were not consistent and some patients had initial benefit that wore off over time, necessitating several operations. Complications, including dysarthria and dysphagia, were not uncommon, especially in bilaterally operated patients.

Concerns about potential side effects of bilateral lesions, and the beneficial effect of GPi DBS on dyskinesias in PD patients, led the group of Coubes in France to propose the use of GPi DBS in dystonia. Their early report of successful treatment has been confirmed in larger series of patients and multicentre controlled trials.

Primary generalized dystonia is recognized as being the indication giving the best results and both *DYT1* positive and negative patients can obtain a good effect – up to 70% improvement of the clinical score has been reported. The improvement is gradual and follows a complex time course; the mobile aspects of the dystonia tend to improve more rapidly than the fixed aspects that can take up to 6 months. In consequence it is difficult to adjust stimulation parameters according to acute changes of symptoms.

Beneficial effect on quality of life has also been reported, while there was little change on cognitive scores and neuropsychiatric measures, in particular on depression. The presence of fixed orthopaedic deformities limits the potential beneficial effect of DBS. Sudden interruption of the stimulation can lead to severe dystonic state in these patients, who may need urgent or prophylactic battery replacement.

Myoclonus dystonia (*DYT11*) can also benefit from GPi DBS. Some forms of secondary dystonia may benefit, but usually not to the same extent as primary dystonia. Pain is one aspect that often improves in those patients. Neuroleptic-induced tardive dystonia may show major benefit with GPi DBS.

The surgical procedure is similar to that used for PD and is usually carried out in one session under general anaesthesia. Side effects are rare and usually reversible by adjustment of electrical parameters.

In conclusion, the posteroventral sensorimotor pallidum is the primary brain target for surgical treatment of dystonia (although we successfully target thalamus in patients with dystonic tremor, with good results). DBS is the method of choice. Results for primary dystonia are better than for secondary; and mobile dystonia benefits more than fixed or tonic dystonia.

Chorea

Chorea is derived from the Greek word 'choreia' meaning a dance. Chorea is a state of excessive spontaneous movements, irregularly timed, randomly distributed and abrupt. Severity may range from restlessness with mild intermittent exaggeration of gesture and expression, fidgety movements of the hands or unstable dance-like gait to a continuous flow of disabling and violent movements. Chorea has many causes which can be simply divided into acquired and inherited. This section summarizes the assessment and investigation of the choreic patient and focuses on the important causes of chorea seen in clinical neurological practice (Table 5.8).

Assessment of chorea

Assessment of the choreic patient depends on directed history and examination (Figure 5.2, Table 5.9), which will determine the appropriate investigations to consider (Table 5.10). Onset and nature of progression are important features. Abrupt or subacute onset is more suggestive of acquired causes. It is important to take a detailed drug history (see below), to ask about recent throat infections (Sydenham's chorea or PANDAS), pregnancy (chorea gravidarum), rashes or joint aches (systemic lupus erythematosus [SLE]), and metabolic history (hyperthyroidism), and to note the symmetry of the chorea, as asymmetric onset suggests a structural or vascular lesion in the contralateral basal ganglia (Figure 5.3). Most inherited causes of chorea have a slow

Table 5.8 Inherited and acquired causes of chorea.

Inherited causes	Acquired causes
Huntington's disease*	Focal striatal pathology:
Neuro-acanthocytosis	Stroke
Macleod syndrome	Space-occupying lesions
Dentatorubro-pallidoluysian atrophy	Drug induced
Benign hereditary chorea	Chorea gravidarum
Spinocerebellar ataxia types 1, 2, 3 and 17	Thyrotoxicosis
Mitochondrial disorders	Systemic lupus erythematosus/antiphospholipid syndrome
Inherited prion disease	Post-infective:
Huntington's disease-like 2	Sydenham's chorea (group A streptococcal infection)
Wilson's disease	Paediatric autoimmune disorders associated with streptococcal infections (PANDAS)
Friedreich's ataxia	Herpes simplex encephalitis
Neurodegeneration with brain iron accumulation type 1	Polycythaemia rubra vera
Ataxia telangiectasia	Infective:
Neuroferritinopathy	AIDS
Lysosomal storage disorders	New variant Creutzfeldt–Jakob disease
Amino acid disorders	
Tuberous sclerosis	

*The most common cause of inherited chorea – the remainder of these disorders are rare.

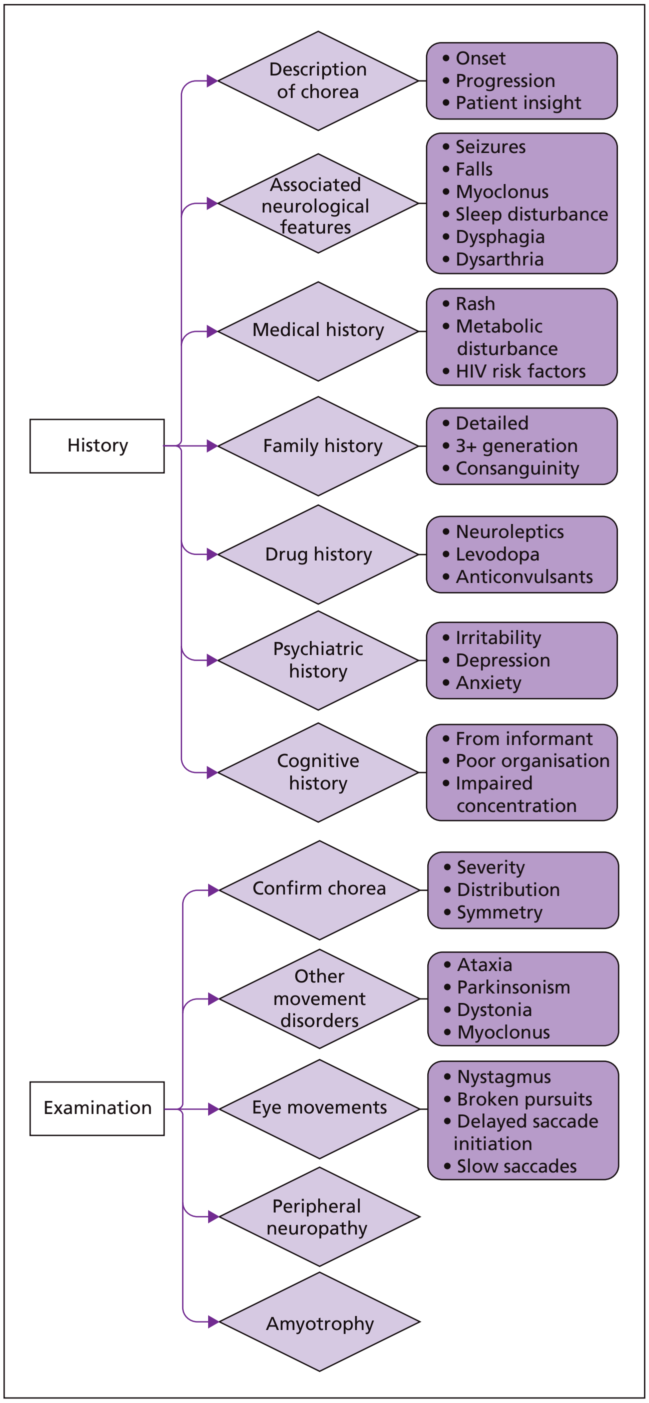
History
Description of chorea
• Onset
• Progression
• Patient insight
Associated neurological features
• Seizures
• Falls
• Myoclonus
• Sleep disturbance
• Dysphagia
• Dysarthria
Medical history
• Rash
• Metabolic disturbance
• HIV risk factors
Family history
• Detailed
• 3+ generation
• Consanguinity
Drug history
• Neuroleptics
• Levodopa
• Anticonvulsants
Psychiatric history
• Irritability
• Depression
• Anxiety
Cognitive history
• From informant
• Poor organisation
• Impaired concentration
Examination
Confirm chorea
• Severity
• Distribution
• Symmetry
Other movement disorders
• Ataxia
• Parkinsonism
• Dystonia
• Myoclonus
Eye movements
• Nystagmus
• Broken pursuits
• Delayed saccade initiation
• Slow saccades
Peripheral neuropathy
Amyotrophy

Figure 5.2 Clinical assessment of the choreic patient.

and insidious onset, most commonly noticed by friends or relatives rather than patients themselves. A detailed family history is crucial and particular attention should be paid to a parent who died at a relatively young age.

Huntington's disease

Huntington's disease (HD) is a slowly progressive autosomal dominant neurodegenerative disorder and the most important inherited cause of chorea. Onset is usually in adult life with a mean age of about 40 years, although juvenile and elderly onset are well described. It progresses inexorably, with death occurring 15–20 years from onset. Prevalence is 4–10/100,000 in populations of Western European descent, but HD has been described throughout the world. HD is named after George Huntington who originally described it in 1872. In 1993, the causative gene defect was identified as a CAG repeat expansion, encoding polyglutamine repeats within a novel protein *huntingtin*. This highly polymorphic CAG repeat is located in exon 1 and ranges between 10 and 28 copies on normal chromosomes, but is expanded to a range of 36–121 on HD chromosomes. Adult onset patients usually have 40–55 repeats, with juvenile onset patients having over 60. CAG repeats above 40 are fully penetrant, although there is a borderline repeat range between 36 and 39 repeats with reduced penetrance.

CAG repeat lengths vary from generation to generation, with both expansion and contraction, but there is a tendency for repeat lengths to increase, particularly when transmitted through the paternal lineage. The instability of the CAG expansion with the tendency to expand during transmission underlies the phenomenon of anticipation. Genetic anticipation describes increasing severity and earlier onset of an inherited disease during intergenerational transmission and is a hallmark of HD and the other trinucleotide repeat disorders. CAG repeat instability

Table 5.9 Neurological examination findings in the choreic patient.

	Peripheral neuropathy	Cerebellar signs	Amyotrophy	Oculomotor dysfunction	Motor impersistence	Tics/vocalizations	Parkinsonism	Dystonia	Myoclonus	Orolingual dystonia	Psychiatric disorders
Huntington's disease				●	●	●	●*	●*	●*		●
Neuro-acanthocytosis	●	●	●			●				●	●
Macleod syndrome	●	●	●			●					●
Friedreich's ataxia	●	●									
Mitochondrial disease	●	●		●				●	●		
Ataxia telangiectasia	●	●		●							
Spinocerebellar ataxias	●†	●		●							●‡
DRPLA		●									
Prion disease		●							●		
Wilson's disease				●		●	●	●			●
NBIA							●	●			
HDL2						●		●	●		●

DRPLA, dentatorubro-pallidoluysian atrophy; NBIA, neurodegeneration with brain iron accumulation.

* Juvenile and Westphal variants of Huntington's disease.

† Typically SCA2.

‡ Typically SCA17.

Table 5.10 Investigations to consider in the choreic patient.

Test	Notes
MRI imaging	Stroke or other focal basal ganglia pathology T2* imaging abnormal in iron accumulation disorders FLAIR imaging abnormal in prion disease Deep brain T2 hyperintensities in Wilson's disease
Full blood count	Haematocrit may be elevated in PRV
Red cell mass	Sensitive test required for diagnosis of PRV
Blood film	3 × fresh thick blood films necessary to exclude neuro-acanthocytosis
Erythrocyte membrane chorein levels (western blot)	Neuro-acanthocytosis
Serum caeruloplasmin	Reduced in Wilson's disease
Urinary copper level	Elevated in Wilson's disease
Liver biopsy	Sometimes required to diagnose Wilson's disease
Pregnancy test	Chorea gravidarum in first trimester
HIV test	(Hemi) chorea/ballism may be presenting feature of AIDS
Erythrocyte sedimentation rate and antinuclear antibody	Sensitive tests to reveal SLE
Anti-dsDNA	Relatively specific to SLE
Anticardiolipin and lupus anticoagulant	Antiphospholipid syndrome is risk factor for chorea
Thyroid function tests	Thyrotoxicosis
Antistreptolysin O (ASO) titre	Recent streptococcal infection suggests Sydenham's chorea/PANDAS
Antibasal ganglia antibodies	Associated with post-infective chorea, chorea gravidarum and OCP-induced chorea
Muscle biopsy	Ragged red fibres or respiratory chain abnormalities in mitochondrial disease
Cerebrospinal fluid analysis	May reveal inflammatory/neoplastic causes

MRI, magnetic resonance imaging; PANDAS, paediatric autoimmune disorders associated with streptococcal infection; PRV, polycythaemia rubra vera; OCP, oral contraceptive pill; SLE, systemic lupus erythematosus.

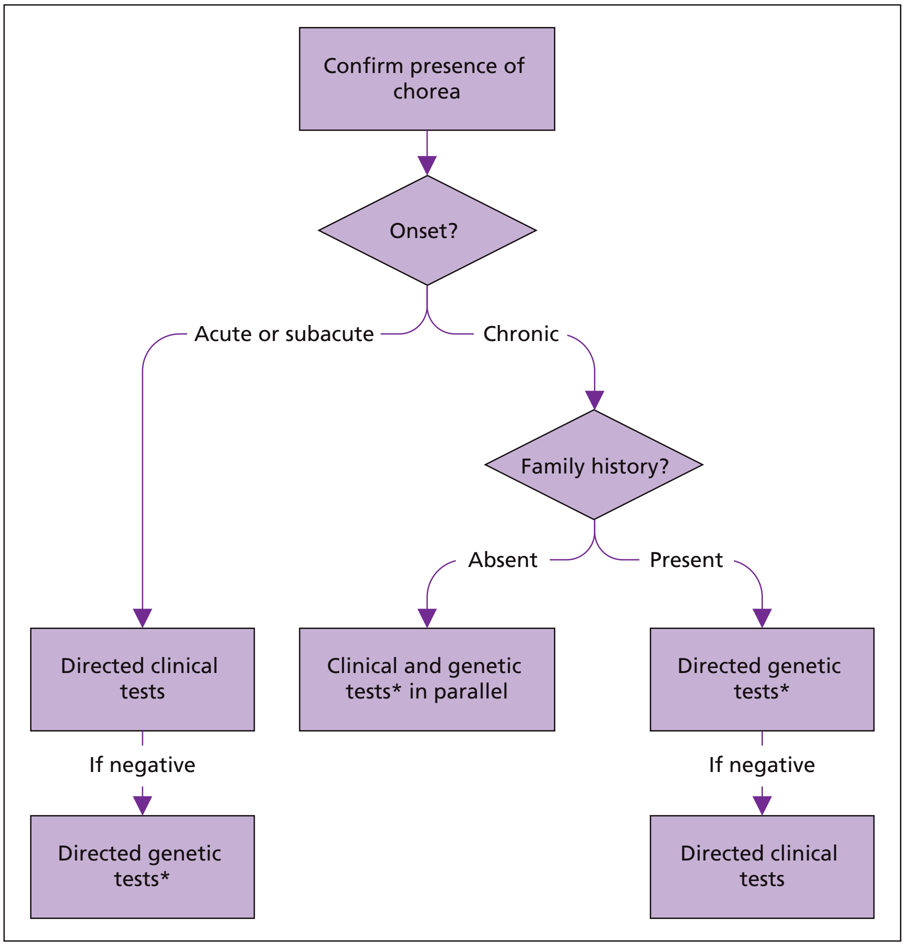
Confirm presence of chorea
Onset?
Acute or subacute
Chronic
Family history?
Absent
Present
Directed clinical tests
Clinical and genetic tests* in parallel
Directed genetic tests*
If negative
If negative
Directed genetic tests*
Directed clinical tests

Figure 5.3 Approach to the investigation of the choreic patient. * Genetic testing must always be preceded by detailed expert genetic counselling.

during paternal transmission is important in the development of large expansions associated with juvenile HD: approximately 80% of juvenile HD patients inherit the HD gene from their father. There is a correlation between CAG repeat size and age at onset, such that the larger the repeat, the earlier the onset. Most individuals with more than 50 repeats develop the disease before the age of 30 years. CAG repeat number also appears to govern the development rate of neuropathological changes. However, CAG repeat length does not completely explain variations in age of onset, clinical phenotype or rate of clinical progression, so that other modifying genes obviously have an important role.

Neuropathologically, in the early stages of disease, the brain can look macroscopically normal, but later there is marked cortical atrophy with ventricular dilatation, severe atrophy of the caudate more than the putamen, with atrophy of the internal segment of the globus pallidus and substantia nigra pars reticulata.

Clinical features

HD can produce a varied clinical phenotype. It is important to realize that as the disease progresses, the signs and symptoms change, so disease duration can markedly modify the clinical presentation.

Motor features

The onset of HD is often difficult to discern clearly. Many patients report psychiatric problems or mild cognitive symptoms before developing any motor problems. However, the definitive diagnosis of HD is usually made when motor abnormalities are noted on examination. Subtle motor abnormalities seen early in the disease include general restlessness, abnormal eye movements, hyper-reflexia, impaired finger tapping, and fidgety movements of fingers, hands and toes during stress or when walking. Oculomotor abnormalities are a cardinal feature of the disease, and often the earliest motor sign. Saccadic abnormalities are characteristic and may include gaze impersistence and distractibility and delayed initiation or slowing of voluntary saccades (vertical worse than horizontal).

As the disease progresses, more obvious extrapyramidal signs develop; chorea is seen in 90% of adult onset patients but may decrease in the late stages, whereas dystonia, rigidity and parkinsonism may dominate the clinical picture in late disease. A key motor abnormality in HD is impaired voluntary motor function with clumsiness, motor impersistence and disturbances in fine motor control and motor speed. Gait disturbance is common, with impaired postural reflexes making patients more prone to falling. Dysarthria and dysphagia are common and should be asked about.

Cognitive features

Cognitive abnormalities are variable but universal in HD. The key cognitive abnormalities seen are impaired executive function with poor planning and judgement, impulsive behaviour, disorganized actions and difficulty coping with multiple tasks. Many patients exhibit psychomotor slowing with apathy, lack of self-care and loss of initiative which can make caring for them difficult. Patients often complain early on of visual and verbal memory problems, in addition to poor concentration and attention.

Psychiatric features

The combination of psychiatric and cognitive features causes the greatest disability, functional decline and distress to relatives and HD patients.

Psychiatric symptoms are common, particularly depression and anxiety. Irritability is also very common and some patients become aggressive. As the disease progresses, obsessions and compulsions often make life difficult for carers. Psychosis, despite being well-recognized, is relatively rare but the suicide rate is much higher than in the general population. Psychiatric symptoms often cause a great deal of distress to patients and relatives and should be actively managed with the same drugs used in standard psychiatric practice.

Juvenile Huntington's disease

Juvenile HD cases are defined as onset before age 20 years, usually associated with repeat lengths greater than 60. They have more severe disease and shorter life expectancy. The akinetic-rigid form of the disease (Westphal variant) is more common in juvenile HD: patients typically have little chorea and are predominantly rigid and dystonic. Juvenile HD patients also have a higher incidence of seizures and myoclonus than adult onset patients. Younger adult-onset patients with HD (<40 years) may also present with a predominantly parkinsonian phenotype similar to the juvenile HD cases.

Differential diagnosis of Huntington's disease

Huntington's disease phenocopies

Before the advent of genetic testing for HD, diagnosis was based on clinical evaluation and neuropathological examination. Now, genetic diagnosis allows definitive confirmation of the disease. Genotype–phenotype studies have increased our understanding of disorders that can present like HD (HD phenocopies) with similar cognitive, psychiatric and motor features, but are HD gene negative (Table 5.11). HD phenocopies occur in approximately 1% of large genetic screens of individuals with clinical signs of HD. An approach to genetic testing of HD phenocopies is suggested in Figure 5.4.

HDL2 (HD-like 2) is caused by a CAG/CTG expansion in the *Junctophilin-3* gene and is very rare, and moreover only reported so far in individuals with African ancestry. In one consanguineous family, a phenocopy syndrome (HDL3) was mapped to 4p15.3, but no causative mutation has been identified. Other dominantly inherited diseases mimicking HD are dentatorubropallidoluysian atrophy (DRPLA), another polyglutamine disorder caused by a CAG repeat expansion in the atrophin-1 gene, and spinocerebellar (SCA) 17 – also called HDL4 – caused by a CAG repeat expansion in the TATA-binding gene (*TBP*). SCA1 and SCA3 (Chapter 16) may also mimic HD. Inherited prion disease may cause HD phenocopies: one mutation causes HDL1, an early onset prion disease with prominent psychiatric features. Neuroferritinopathy, a very rare, dominantly inherited disorder, caused by mutations in the ferritin light chain, has clinical features overlapping with HD.

Neuro-acanthocytosis

There are several conditions (the neuro-acanthocytoses) in which chorea and other movement disorders are associated with the presence of acanthocytosis of the red blood cells in the peripheral blood. Autosomal recessive neuro-acanthocytosis is rare, and associated with mutations in the *CHAC* gene leading to production of a truncated protein termed chorein. Onset is typically in the fourth decade with a progressive movement disorder, psychiatric and cognitive changes which mimic HD. The movement disorder comprises chorea, dystonia and tics, with prominent eating dystonia, dystonic tongue protrusion and tongue and lip biting. Psychiatric and cognitive features are similar to HD. Unlike HD, seizures are seen in 50% of patients, and there is commonly a distal amyotrophy or axonal neuropathy with a high creatine kinase. Investigations include analysis of fresh blood films for >3% of acanthocytes. More than one blood film may be necessary to identify these. Genetic testing for mutations in the CHAC gene is difficult, so confirmation relies on demonstration of low erythrocyte membrane chorein levels in the blood.

Table 5.11 Differential diagnosis of Huntington's disease (HD phenocopies).

Condition	Cause
HDL1	Octapeptide repeat insertion in gene encoding prion protein
HDL2	Triplet repeat expansion in gene encoding junctophilin-3
HDL3	Causative mutation unidentified
SCA17 (HDL4)	Triplet repeat expansion in gene encoding TATA-box binding protein
Inherited prion disease	Mutations in gene encoding prion protein
SCA1	Triplet repeat expansion in gene encoding ataxin-1
SCA3	Triplet repeat expansion in gene encoding ataxin-3
DRPLA	Triplet repeat expansion in gene encoding atrophin-1
Neuro-acanthocytosis	Mutation in gene encoding chorein
Neuroferritinopathy	Mutations in gene encoding ferritin light-chain
NBIA	Mutations in the *PANK2* gene

DRPLA, dentatorubro-pallidoluysian atrophy; NBIA, neurodegeneration with brain iron accumulation.

Macleod syndrome is a very rare X-linked recessive disorder linked to mutations in the *XK* gene, which encodes the Kell antigen. It usually begins around the age of 45 years and is slowly progressive, with limb chorea and facial tics. Dystonia is less common than in chorea-acanthocytosis and subcortical dementia and psychiatric features tend to occur later in the disease. Axonal neuropathy, cardiomyopathy and haemolytic anaemia may be seen, CPK is often elevated, and acanthocytes are usually found in fresh thick peripheral blood films.

Acanthocytes have also been described in pantothenate kinase-associated neurodegeneration (PKAN, or NBIA type 1) and HDL2 and all these disorders are encompassed under 'core neuro-acanthocytosis syndromes'.

Post-streptococcal autoimmune disorders

Sydenham's chorea and PANDAS (paediatric autoimmune disorders associated with streptococcal infection) may both present with chorea and neuropsychiatric manifestations. Sydenham's chorea is one of the major manifestations of rheumatic fever. It occurs in children, mainly girls, between 5 and 15 years of age and is now rare in the developed world. Widespread chorea, behavioural disturbance and obsessive-compulsive symptoms are common. It is self-limiting and usually resolves within 6 months, with about 20% of cases being recurrent. Antibasal ganglia

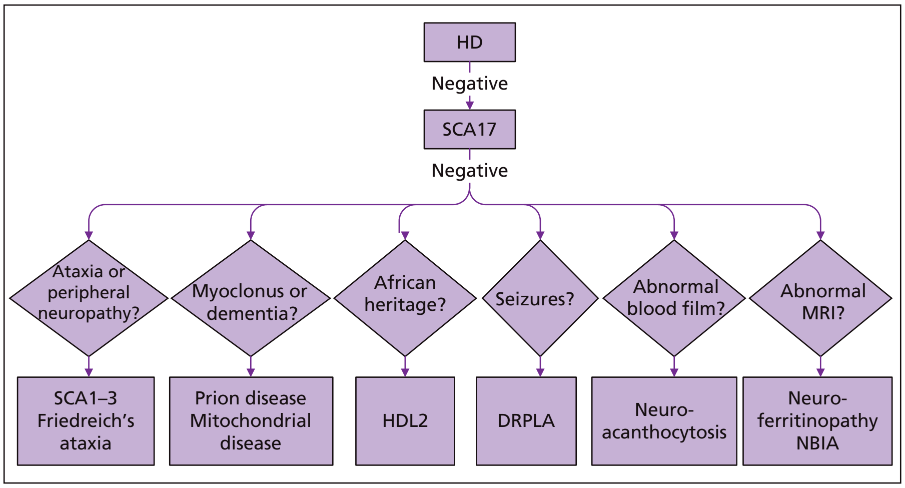

Figure 5.4 Suggested approach to genetic testing in chorea.

antibodies can be detected. The mechanism of damage is thought to be molecular mimicry with cross-reaction between antistreptococcal antibodies and neurones in the basal ganglia. PANDAS is also discussed under tics.

Benign hereditary chorea

Benign hereditary chorea (BHC) is a very rare, dominantly inherited disorder caused by mutations in the gene encoding thyroid transcription factor 1 (*TITF1*). It is usually of early onset and is characterized by very slowly progressive chorea without cognitive decline or other neurological features, but there is clinical heterogeneity within and between families. Some cases of BHC also display dystonia, myoclonic jerks, mild dysarthria, gait disturbances or low–average intelligence, and many cases may also have hypothyroidism or pulmonary abnormalities of varying degrees, leading to the recent application of the term 'brain–thyroid–lung syndrome'.

Drug-induced chorea

Many different medications can cause chorea. The main ones include neuroleptics (tardive dyskinesia), levodopa/dopamine agonists/anticholinergics (most often, but not exclusively, in patients being treated for parkinsonism), anticonvulsants (phenytoin, carbamazepine, valproate, gabapentin), CNS stimulants (amphetamines, methylphenidate, cocaine), benzodiazepines, oestrogens (oral contraceptive pill or, rarely, hormone replacement therapy) and lithium (although this more commonly causes myoclonus or jerky tremor).

Drug management of chorea

Chorea can cause cosmetic embarrassment to some patients but many do not notice the severity of their chorea. Indeed, it is often relatives, rather than patients, who request treatment. Best agreed practice is to use antichoreic medication sparingly as no drug is particularly efficacious, and a balance has to be struck between benefits and side-effects. For functionally disabling chorea, drugs such as sulpiride, olanzapine, risperidone and tetrabenazine may be useful by non-specifically damping down movements in general, but they can worsen speech, swallowing and gait and balance, so need careful monitoring.

Tics

Tics are typically relatively brief rapid intermittent purposeless involuntary movements (motor tics) or sounds (vocalizations). Classically, they can be suppressed, at least temporarily, by an effort of will, but at the expense of rising inner tension, often followed by a rebound exacerbation. Most tics are abrupt in onset and duration (clonic tics), but may also be slow and sustained, either dystonic (associated with more sustained muscle contractions) or tonic (if muscle contractions are not associated with any movement, e.g. arm or abdominal tensing).

Gilles de la Tourette syndrome

Gilles de la Tourette syndrome (GTS) is the most common cause of tics. The diagnostic criteria for GTS include multiple motor tics and one or more phonic and/or vocal tics, which must last longer than a year. The motor and phonic tics do not necessarily occur together, characteristically wax and wane over time, occur in bouts and are suggestible and suppressible. The maximum age at onset is 18 years. The mean age at onset of motor tics is about 7 years, and vocal tics 11 years, the worst severity is at 10–12 years, and the majority of symptoms disappear in half of the patients by the age of 18 years. Associated behaviours such as obsessive-compulsive behaviour or obsessive-compulsive disorder (OCB/OCD) may be more evident later.

Tics in GTS can be simple (e.g. blinking, eye rolling, head nodding, facial grimacing) or complex (e.g. touching, squatting). Premonitory sensations (also referred to as premonitory urges, mental urges or inner tension) precede both motor and phonic tics in up to 80% of patients; these may be localized (burning feeling in the eye before an eye-blink, or a sensation similar to nasal stuffiness before a sniff – the sensation has been likened to that which occurs before a sneeze). They may be localized (around the area of the tic) or generalized (covering a wide area of the body). New tics may appear in response to a new somato-sensory sensation, such as a cough (phonic tic) persisting after an upper respiratory tract infection. Tics usually begin in the head and face, and blinking is one of the most common first tics. Simple phonic tics include sniffing, throat clearing, gulping, snorting and coughing. Complex vocal tics include barking, the making of animal noises, inappropriate voice intonations and uttering strings of words. Tics characteristically are suggestible, suppressible, there is rebound after suppression and they have a waxing and waning course. Other important and characteristic features of GTS include echolalia (copying what other people say), echopraxia (copying what other people do) and palilalia (repeating the last word or part of sentence said by the individual). Coprolalia (inappropriate involuntary swearing, often disguised by the patient) is uncommon, occurring in only 10–15%, starting at around 15 years. Many clinicians are under the misapprehension that coprolalia must be present in order to make the diagnosis. Instead of the whole swear word, many individuals say only parts of the word and disguise it (by coughing, saying something, covering their mouths). Copropraxia (e.g. the V sign) may also occur but is rare.

Epidemiology, history and prevalence

GTS has been described worldwide but with apparent different prevalence rates. The male : female ratio is 3 : 1. Clinical characteristics are similar irrespective of the country of origin. In some instances it seems that within families, the affected males have tic symptoms, whereas the females often have OCB. GTS was once considered to be uncommon. However, recent studies report a prevalence of 0.4–3.8% for youngsters aged 5–18 years, and most recently a figure of 1% worldwide overall prevalence has been calculated. The prevalence of GTS in special educational populations (individuals with learning difficulties) or autistic spectrum disorders can be as high as 6–10%. It is important to note that GTS individuals identified in community settings have more behavioural, mental health and educational difficulties than their peers. Many people with GTS never come to medical attention. Among those who do, the correct diagnosis is often missed as many clinicians remain under the misapprehension that coprolalia is necessary for the diagnosis.

Psychopathology and associated co-morbidity

About 90% of GTS individuals have psychiatric co-morbidity. The most common is attention deficit hyperactivity disorder (ADHD), followed by OCB and OCD. Checking rituals, 'evening up', counting rituals and compulsions to touch objects or people may be present, but are not often volunteered and need to be asked about. Anger control problems, sleep difficulties, coprolalia and self-injurious behaviours (SIB) are more common in those with co-morbidity. Patients with GTS have more depression, anxiety, hostility, obsessional symptomatology and personality disorders than controls. Individuals with GTS only appear to be different to those with GTS together with ADHD.

Assessment

GTS is a clinical diagnosis. Standardized schedules are available to describe the phenomenology, and quantify and qualify associated behaviours and psychopathology, and to monitor response to treatment. Investigations are usually not necessary, but may be helpful in diagnosing alternative causes of tics (see below).

Current aetiological theories

Various causes have been postulated including genetic influences, neuro-immunological reactions to infections, and prenatal and peri-natal difficulties. Complex segregation analysis suggested that GTS was genetic, consistent with a single major gene and autosomal dominant transmission, but with incomplete penetrance. However, much of the genome has been excluded, so the genetics of GTS is much more complicated than previously thought. The term PANDAS (paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) was recently coined for children with post-streptococcal OCD and tics. This pathogenic mechanism is somewhat controversial but most centres that have sought them have also found antibasal ganglia antibodies (ABGAs) in a subgroup of patients with GTS. Streptococcal infection (with group A beta-haemolytic strains) probably does not cause GTS, but individuals may inherit a susceptibility to GTS and to the way they react to some infections.

Multiple phenotypes of GTS

Many non-expert clinicians prefer not to make a diagnosis of GTS when the patient presents with only simple motor and phonic tics, when they simply call it a 'tic disorder'. However, several recent studies have demonstrated by hierarchical cluster analysis or principal component factor analysis that there is more than one type of GTS. Moreover one factor (phenotype), replicated by several centres, consists almost solely of simple motor and phonic tics. Other factors include complex tics and associated psychopathologies, as well as aggressivity and SIB. There have been initial suggestions that the varying phenotypes may have different aetiologies.

Other forms of tic disorder

Tic disorders, usually referring to motor tics, are much more common than GTS, although prevalence figures differ, depending on the population studied. They have been reported to occur with a point prevalence of 1–29% of young people. The most common tic disorders can be divided into the following:

1 Transient tic disorder (TTD), in which there are single or multiple motor and vocal tics occurring for at least a month but for no longer than a year;

2 Chronic motor or vocal tic disorder (CMTD), in which motor or vocal but not both have been present in excess of a year; or

3 Tic disorder not otherwise specified, such as adult onset tic disorder with an age at onset after 18 years.

Once again, tics are more frequent in those individuals with behavioural difficulties, learning difficulties, and those requiring special education placement or those seen as 'problem children'.

Other diseases that can cause tics

Tics may also be seen in WD, neuro-acanthocytosis, Lesch–Nyhan syndrome, neuroferritinopathy, autism spectrum disorders, and in association with acquired lesions of the caudate nucleus and after chronic neuroleptic drug intake. However, they are usually only a part of the clinical picture, so should not be confused with primary tic disorder. Not all vocalizations are tics – they can be seen in dystonia, HD and tardive dyskinesia, for example.

Investigation of tics

In the typical case (the vast majority) no investigations are necessary. If the presentation is unusual, the following could be helpful: serum copper and coeruloplasmin and slit-lamp examination for WD; ASO titre, throat swab, anti-DNA antibodies and ABGAs for post-streptococcal tics; fresh thick blood films (×3), creatine phosphokinase, nerve conduction studies, MRI, chorein and ChAc gene testing for neuro-acanthocytosis.

Management of GTS and tics

In mild cases, explanation, reassurance and psycho-education may be the only interventions required. When the condition is causing problems, supportive psychotherapy, cognitive–behavioural therapy (CBT) and more recently documented habit reversal training (HRT) may be useful: HRT specifically targets tics. Ideally, management should be multidisciplinary and treatment should be targeted at symptoms.

In many patients, medication may be required for the treatment of the tics and psychopathologies. The main agents for the tics are the typical and atypical neuroleptics, given in small doses (relative to treating psychosis), e.g. haloperidol 0.5–3 mg/day or sulpiride 100–400 mg/day. The older 'typical' neuroleptics such as haloperidol, pimozide, sulpiride and tiapride, and the newer 'atypical' neuroleptic such as risperidone have all been shown to be superior to placebo in double-blind trials. Tetrabenazine can also be effective but can often cause depression. Clonidine or guanfacine can help tics, impulse control or ADHD. If these agents are used, baseline ECG is advisable, as is regular monitoring of pulse and blood pressure. Recently the newer 'atypical' neuroleptics (risperidone, quetiapine, aripiprazole) as well as sulpiride and tiapride are becoming more popular because of the unacceptable side effects of the older agents. The response to medication in GTS patients is idiosyncratic. Importantly, individuals with this often lifelong, generally benign, condition should be warned of the possibility of developing a superimposed tardive movement disorder after chronic treatment with neuroleptic drugs.

Antidepressants, especially SSRIs, are useful for depression (using the standard dose, e.g. fluoxetine 20 mg), whereas the dose for OCB/OCD is higher (e.g. 40–60 mg). Clomipramine (a tricyclic) may be useful in OCB/OCD, but usually has more side effects than the SSRIs and is dangerous in overdose. SSRIs have been reported to cause suicidal ideation and there are now strict guidelines for the use of SSRIs in young people. In some patients, botulinum toxin injections to the affected areas (e.g. vocal cords if loud distressing vocal tics/coprolalia) can improve the tics and the urge to tic. DBS of internal capsule, GPi or thalamus in some carefully selected, severely affected and treatment-resistant patients has apparently helped.

When a patient has GTS + ADHD, one should assess which symptoms are most problematic, and attempt to treat these. Clonidine helps tics, ADHD and sleep. It was once thought that stimulants (e.g. methylphenidate) that improve ADHD increased tics, and were therefore contraindicated, but this is now known not to be the case in most patients. Newer once-daily slow-release preparations may increase compliance. If the ADHD and tics pose equal difficulties, try clonidine; if ADHD is the greatest problem, try stimulants. The next option is to use stimulants with clonidine. Stimulants may also be given with neuroleptics.

Myoclonus

Myoclonus comprises sudden brief shock-like involuntary movements caused by muscular contractions or inhibitions. Muscle contraction produces positive myoclonus and muscle inhibition causes negative myoclonus or asterixis (e.g. liver flap). Myoclonus can be focal, multifocal, generalized, spontaneous or reflex. It may occur at rest, when maintaining a posture or during action. Myoclonus can be classified as cortical, subcortical, spinal or peripheral, based on the presumed physiological mechanism underlying its generation. Alternatively, based on its aetiology, it can be classified as physiological, essential, epileptic or symptomatic (Table 5.12).

Physiological myoclonus

This includes hypnic jerks (initial phases of sleep), hiccup (physiological myoclonus of diaphragm) and startle response (commonly exacerbated by anxiety).

Essential myoclonus

See section on myoclonus-dystonia (DYT11) above in dystonia section.

Epileptic myoclonus

This term is used to denote conditions where myoclonic jerks are part of an epileptic syndrome (see Neurophysiological assessment below and Chapter 6). Generalized myoclonus can occur in the syndromes of idiopathic generalized epilepsy or in the secondarily generalized epilepsies which include the progressive myoclonic epilepsies or the static epileptic encephalopathies. Epileptic myoclonus is accompanied by generalized epileptiform discharges, but the myoclonus itself may be focal, segmental or generalized. Focal myoclonus can occur in secondary symptomatic epilepsy as a result of infection, inflammation, vascular disease, trauma or tumours.

Familial cortical tremor (also called benign autosomal dominant familial myoclonic epilepsy)

Clinically, this superficially resembles essential tremor. It is associated with infrequent or rare generalized seizures. It is an autosomal dominant, benign condition characterized by fine shivering-like 'tremor'. It usually presents in the third or fourth decade of life and there is no significant clinical progression. The myoclonus usually responds to valproate, carbamazepine or primidone, and has been mapped in Japanese families to chromosome 8q and in Italians to chromosome 2p.

Epilepsia partialis continua

This is spontaneous, regular or irregular muscle twitching of cortical origin confined to one part of the body and continuing for a period of hours, days or weeks. This condition is further described in Chapter 6.

Secondary myoclonus

This occurs in the context of an underlying neurological or non-neurological disorder brought about by trauma, brain hypoxia or progressive myoclonic encephalopathies. Often there is clinical or pathological evidence of diffuse or focal nervous system involvement.

Non-progressive myoclonic encephalopathies

It is important to recognize metabolic causes (renal or hepatic failure, vitamin E deficiency, increased level of antithyroid autoantibodies), toxic causes (bismuth, methyl-bromide, tethraethyl, chloralose poisoning) or drugs (levodopa, lithium, tricyclic antidepressants, morphine, antibiotics, SSRIs, MAOIs, antipsychotic and anaesthetic agents) that may cause myoclonus. Usually such myoclonus is multifocal and often stimulus-sensitive, and may include negative myoclonus.

Table 5.12 Classification of myoclonus. (From Caviness & Brown (2004) with permission.)

I. Physiological myoclonus
Sleep jerks (e.g. hypnic jerks)
Hiccough (singultus)

II. Essential myoclonus (+/– dystonia)
Hereditary (autosomal dominant)
Sporadic

III. Epileptic myoclonus
***Progressive myoclonic epilepsy* (*PME*)**
Mitochondrial disease
Lafora body disease
GM2 gangliosidosis (Tay–Sachs disease)
Ceroid lipofuscinosis (Batten/Kufs disease)
Sialidosis

***Progressive myoclonic ataxia** (*PMA*)**
Mitochondrial disease
Unverricht–Lundborg disease
Spinocerebellar degenerations
Coeliac disease

Other myoclonus epilepsy
First year of life:
  Infantile spasms
2–6 years:
  Lennox–Gastaut syndrome
Older children and adolescents (and adults)
  Photosensitive epileptic myoclonus
  Myoclonus absences
  Juvenile myoclonic epilepsy
Epilepsia partialis continua
Cortical reflex myoclonus

IV. Symptomatic myoclonus
A. Storage diseases
See III (above) PME

B. Spinocerebellar degenerations
Friedreich's ataxia
Ataxia-telangiectasia

C. Other degenerations
Basal ganglia degenerations
Wilson's disease
Dystonia
Hallervorden–Spatz disease
Huntington's disease
Multiple system atrophy
Cortico-basal degeneration
Dentatorubro-pallidoluysian atrophy (DPRLA)

D. Dementias
Creutzfeldt–Jakob disease
Alzheimer's disease,
Dementia with Lewy bodies
Parkinson's disease dementia
Frontotemporal dementia

E. Infectious or post-infectious
Subacute sclerosing panencephalitis
HIV
Post-infectious encephalitis

F. Metabolic
Hyperthyroidism
Hepatic failure
Renal failure
Dialysis syndrome
Hyponatraemia
Hypoglycaemia
Non-ketotic hyperglycaemia
Biotin deficiency
Mitochondrial disease

G. Malabsorption
Coeliac disease
Whipple's disease

H. Toxic and drug-induced syndromes

I. Physical encephalopathies
Post-hypoxic action myoclonus (Lance–Adams)
Post-traumatic

J. Paraneoplastic encephalopathies
K. Opsoclonus-myoclonus syndrome
Idiopathic
Paraneoplastic
Infectious

L. Focal nervous system damage
Post-stroke
Post-thalamotomy
Tumour
Trauma
Inflammation

M. Exaggerated startle syndrome
Hereditary/sporadic/secondary

N. Palatal myoclonus (tremor)
Idiopathic/symptomatic

O. Spinal myoclonus
Segmental
Propriospinal

P. Peripheral nervous system
Hemifacial spasm

Q. Psychogenic myoclonus

* Myoclonus and cerebellar features main problem, perhaps with mild mental impairment and epilepsy.

Postanoxic action myoclonus (Lance–Adams syndrome)

This is a distinct condition secondary to severe cerebral hypoxia (usually after respiratory rather than cardiac arrest) characterized by action myoclonus, usually without other neurological disturbances, after a latent interval of 24–28 hours (Chapter 19). Myoclonus may be positive, triggered by movement, or negative when the limbs are outstretched against gravity. The voice may be fragmented by the myoclonic jerks. It can be multifocal or generalized. It is most commonly cortical reflex myoclonus, but reticular reflex myoclonus and exaggerated startle may also occur. With treatment using clonazepam, sodium valproate or piracetam or levetiracetam, distal myoclonus can be greatly improved, but asterixis in proximal leg muscles ('bouncy legs') may continue to render the patient wheelchair-bound.

Opsoclonus-myoclonus

This is a well-delineated syndrome that most often occurs in children with neuroblastoma (a tumour that can remit without treatment) or medulloblastoma, or in adults in association with small cell carcinoma of the lung, breast carcinoma or melanoma. It also may be post-infectious or metabolic (coeliac disease) or drug-related. This syndrome is characterized by rapid involuntary saccadic eye movements (opsoclonus) and sudden involuntary muscle contractions (myoclonus). Ataxia is quite often also present. This syndrome is thought to be mediated by autoantibodies directed against onconeural antigens that are expressed by the tumours and also by neurones. Treatment of the underlying cause often leads to an improvement in the syndrome. In idiopathic cases, steroids and/or immuno-modulatory treatment have been used with some success.

Myoclonus in neurodegenerative disorders

Cortical myoclonus is present in about 15% of patients with DLB or PD-D but is uncommon in PD patients without dementia.

Patients with MSA often display irregular small-amplitude myoclonic movements (mini-polymyoclonus) of the hands and/or fingers on posture (jerky postural tremor) that are stimulus-sensitive, or occur during voluntary movements. A cortical origin can often be demonstrated by back-averaging techniques, and somato-sensory evoked potentials (SSEPs) are sometimes 'giant'.

Myoclonus occurs in most patients with CBD, usually appearing focally in the arm and less commonly in the legs, together with other manifestations such as apraxia, rigidity, dystonia and alien limb phenomenon. It may occur in repetitive rhythmic fashion (jerky tremor) at rest and more commonly when attempting to activate the arm or following somato-sensory stimulation (reflex myoclonus). A cortical origin has been postulated. In contrast to CBD, myoclonus is rare in progressive supranuclear palsy (PSP), another tauopathy.

HD can rarely be associated with myoclonus, usually in individuals with a juvenile onset and longer CAG repeats. Myoclonus is more common in DRPLA, when it is usually associated with epilepsy.

In Alzheimer's disease, myoclonus is usually multifocal but can also be generalized. There can be sporadic large myoclonic jerks or repetitive small ones which may occur at rest, during action or be stimulus-sensitive. Commonly, myoclonus appears in middle and late stages of the disease, affecting about 50% of patients. It may occur at the onset of the disease in patients with earlier age of onset, rapid progression and in familial causes of Alzheimer's disease.

Myoclonus has recently been described in some patients with fronto-temporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). Myoclonus is often observed (82–100%) in sporadic, familial and new-variant Creutzfeldt–Jakob disease (CJD) during the course of the disease, in which the jerks are often diffuse, generalized, relatively rhythmic and associated with periodic sharp-wave EEG activity (1–1.5 Hz). They are stimulus-sensitive and can persist during sleep.

Subcortical myoclonus

Rhythmic myoclonus in a brainstem or spinal segmental distribution suggests a focal lesion at or near that segment of the brainstem or spinal cord. Generalized jerks most commonly reflect an origin in the brainstem reticular formation while axial jerks usually suggest a spinal cord lesion.

Startle syndromes

The startle reflex is a bilaterally synchronous shock-like set of movements evoked by sudden stimuli. Its most prominent features are forceful closure of the eyes, raising of flexed arms above the head, and flexion of the neck, trunk, elbows, hips and knees. The auditory startle reflex originates in the caudal brainstem, more specifically in the bulbo-pontine reticular formation. The nucleus reticularis pontis caudalis seems particularly important. Startle syndromes occur in three different groups of disorders with abnormal response to startling events: hyperekplexia, neuropsychiatric startle syndrome and startle-induced epilepsy.

The major form of hyperekplexia is characterized by generalized stiffness noticeable soon after birth, but subsiding during the first years of life, excessive startling to an unexpected stimulus that remains throughout life, and generalized stiffness in response to startle that lasts a few seconds and which commonly produces a fall forwards 'as stiff as a board' while fully conscious. In this form, mutations in the $\alpha 1$ subunit of the glycine receptor gene, *GLRA1*, or related genes have been identified. A minor form of hyperekplexia is characterized by excessive startle only, with latencies of muscle activation longer than in the major form. No definite genetic substrate for this form has been found. Excessive startle also occurs in the context of neuropsychiatric conditions such as anxiety, panic attack, post-traumatic stress disorders or culture-specific disorders such as the jumping Frenchmen of Maine.

Startle epilepsy is an asymmetric tonic epileptic seizure typically induced by a sudden stimulus, mostly observed in young patients with infantile cerebral hemiplegia.

Palatal myoclonus

See under Palatal tremor, above.

Spinal myoclonus

Segmental myoclonus involves one or two contiguous spinal segments, whereas in proprio-spinal myoclonus several segments are involved because electrical activity spreads upwards and downwards from a spinal generator via slower proprio-spinal pathways. Spinal myoclonus has been reported in association with spinal cord trauma, vascular disease, disc herniation, drugs and infection. It is usually rhythmic or periodic, involving muscles belonging to one or two spinal segments.

Proprio-spinal myoclonus may also be rhythmic or arrhythmic but is characterized by axial jerks with flexion of the trunk and limbs. It occurs mainly when the patient is relaxed, predominantly when lying on a bed or falling asleep, and may be a cause of insomnia. Jerk duration is usually longer and more variable (50–1000 ms) than in cortical myoclonus.

Peripheral myoclonus

Peripheral myoclonus is rare and characterized by rhythmic or semi-rhythmic myoclonus secondary to nerve, root or anterior horn cell disease. Hemifacial spasm is the most common example. Peripheral myoclonus can be also multifocal in anterior horn cell disease (as in post-polio syndrome).

Psychogenic myoclonus

Psychogenic myoclonus can occur spontaneously or following an external insult. It may be focal (restricted to a few muscles or limb) or generalized. Jerks usually have an inconsistent character over time, occasionally associated with other unusual neurological symptoms, with sudden onset and offset. There is often underlying psychopathology, the jerks are commonly distractible and may respond to placebo or psychotherapy (see also under Other movement disorders below).

Drug-induced myoclonus

Many different drugs can cause myoclonus. These include antidepressants (especially SSRIs), opiates, antiparkinsonian medications, some antibiotics (especially quinolones), lithium, bismuth, neuroleptics, anaesthetic agents (especially propofol), cholinesterase inhibitors and, perhaps surprisingly, anxiolytics (especially benzodiazepines) and anticonvulsants.

Treatment of myoclonus

The treatment of myoclonus depends upon the underlying disorder. Depending upon its aetiology, myoclonus can be partially or totally reversed, as in drug-induced or metabolic myoclonus, or surgically treatable lesions. Unfortunately, treatment of the underlying disorder is not always feasible.

Most causative conditions are poorly responsive to pharmacological treatment and often require polytherapy but this may cause side effects such as ataxia and drowsiness.

In cortical myoclonus, sodium valproate is particularly effective, possibly by increasing cortical GABA concentrations and potentiating GABAergic post-synaptic inhibitory activity. Benzodiazepines and barbiturates are also effective and believed to facilitate GABAergic transmission: clonazepam is the most useful antimyoclonic agent. Primidone and phenobarbital are occasionally useful. Piracetam and levetiracetam have been shown to be very useful agents although at the moment limited controlled studies are available. Lamotrigine may be effective alone.

Myoclonus dystonia responds partially to clonazepam, which is also particularly useful in hyperekplexia and in spinal myoclonus. Bilateral pallidal DBS can help severe myoclonus dystonia. Injection of botulinum toxin can help in palatal myoclonus and in hemifacial spasm.

Other movement disorders

Psychogenic movement disorders

Psychogenic movement disorders (PMD) can present as any movement disorder, although dystonia and tremor are the most common manifestations and psychogenic parkinsonism and chorea are rare. PMD represent 4–25% of all new cases seen in specialist movement disorders clinics.

The diagnosis of a PMD is primarily clinical, although investigations to exclude alternative diagnoses, and specific electrophysiological tests for certain forms of PMD, may have an important role. However, PMD is not simply a diagnosis of exclusion, and positive features suggesting the diagnosis should be sought. These include marked fluctuations during examination; distractibility; increase with attention or suggestion; incongruence with patterns of recognized movement disorders; the presence of other non-organic signs or a psychiatric disorder; discrepancy between objective signs and disability; abrupt onset with rapid progression to maximum severity; inconsistency over time; a history of previous somatizations; and a sustained and substantial response to placebo or psychotherapy. While none of these features is pathognomonic, they allow a classification based on degree of diagnostic certainty (Table 5.13).

Specific PMDs may have additional clinical and investigational features that support the diagnosis. In psychogenic tremor these include co-activation of antagonist muscles; entrainability of tremor to the frequency of contralateral hand movements; and an increase of amplitude or change of tremor frequency when the limb is loaded with a weight. In psychogenic myoclonus the presence of a Bereitschaftspotential (premovement potential) preceding myoclonic movements, of prolonged or variable duration EMG-bursts, and of long latency and variable recruitment in stimulus-sensitive myoclonus all support the diagnosis.

However, in some cases investigations may exclude a psychogenic cause. Thus, in myoclonus, consistent duration of myoclonic bursts less than 70 ms or latency to stimulus-sensitive myoclonus of less than 70 ms or the presence of giant SEPs or cortical correlates of myoclonic jerks on back-averaged EEG exclude a psychogenic aetiology. Similarly, an abnormal DaT SPECT scan excludes a diagnosis of psychogenic parkinsonism. However, the specificity of many tests that are reported to be abnormal in certain movement disorders, e.g. reciprocal inhibition in dystonia, is currently unknown and these tests cannot therefore be relied upon to differentiate them from PMD. In addition, many classic features of movement disorders, e.g. geste

Table 5.13 Diagnostic criteria for psychogenic dystonia. As only the first two categories provide a clinically useful degree of diagnostic certainty they have been combined to one category of 'Clinically definite'.

Documented	Persistent relief by psychotherapy, suggestion or placebo has been demonstrated, which may be helped by physiotherapy, or the patient was seen without the dystonia when believing him or herself unobserved
Clinically established	The dystonia is incongruent with classic dystonia or there are inconsistencies in the examination, plus at least one of the following three: other psychogenic signs, multiple somatizations or an obvious psychiatric disturbance
Probable	The dystonia is incongruent or inconsistent with typical dystonia, or there are psychogenic signs or multiple somatizations
Possible	Evidence of an emotional disturbance

antagoniste in dystonia or treatment-induced dyskinesias in PD, can be seen in PMD. The perceived difficulty of imitating a movement disorder is not sufficient to exclude this diagnosis, and this is exemplified in rare cases of psychogenic palatal tremor. Nevertheless, a diagnosis of PMD should not be made simply because the movement disorder is bizarre. Sometimes it is necessary to observe the patient over time to reach a diagnosis.

The prognosis of long-standing PMD is generally poor, although patients with PMD presenting soon after onset appear to have a better prognosis. Management of PMD is often difficult but should include thorough initial investigations followed by discussion of the diagnosis in a clear but unconfrontational manner emphasizing the unconscious origin of PMD. Where appropriate, exploration of psychiatric disorders or psychological factors underlying the disorder, appropriate referral for diagnosis and treatment, initiation of pharmacological and physical therapy, and continued follow-up by a multidisciplinary team (including the neurologist) should be considered. Avoiding both unnecessary drug treatment and perpetuating illness beliefs are clearly important management goals, particularly in complex and long-standing cases.

Movement disorders associated with dopamine receptor blockade or dopamine depletion

Dopamine receptor blocking drugs are commonly used for psychiatric indications (neuroleptics) but also in the treatment of nausea, vomiting, vertigo, unsteadiness and migraine. Dopamine depletors originally included reserpine (for hypertension), but now only tetrabenazine (for hyperkinetic movement disorders) is licensed. All of the following types of movement disorder can be produced by any of these drugs, except that tetrabenazine does not cause tardive movement disorders.

Drug-induced parkinsonism (DIP) occurs frequently. Often mild, it can nevertheless sometimes be severe, and can be asymmetrical. It is reversible, the vast majority of cases remitting within weeks to 3 months, and a dwindling residual between 3 and 12 months of stopping the offending drug. The longer the duration of parkinsonism after withdrawal of the causative drug, the greater the chance that the individual was already in the early stages of PD (or other parkinsonian disorder). Management is to withdraw the causative agent if possible, and if not, to substitute an atypical neuroleptic drug with less anti-D2 dopaminergic effect. Anticholinergics can help. So too can levodopa, but this risks psychiatric relapse, and has limited effectiveness until the causative drug is withdrawn. DaT SPECT scan is normal in pure DIP.

Acute dystonic reactions affect about 2% of individuals exposed to these drugs. They arise within hours of starting the medication and predominantly affect head and neck, with oculogyria and jaw and neck dystonia, sometimes painful. They spontaneously subside over hours, but within seconds to minutes after IV administration of a centrally acting anticholinergic.

Akathisia ('not sitting') can occur early or late in treatment (the latter, tardive akathisia, can persist after drug withdrawal). The patient has an inner compulsion to move, a 'motor restlessness' that causes them to pace up and down or shift from one foot to the other, with rather stereotyped movements. Treatment is unsatisfactory.

Tardive dyskinesia arises after weeks, months or years of treatment, but persists for a variable time period, sometimes permanently. It can begin, or worsen temporarily, after discontinuing the offending drug. Most cases display relatively rapid, predominantly choreiform buccolinguomasticatory movements, with lip-smacking and sometimes tongue protrusion. These are more common with increasing age and female sex.

Tardive dystonia, more common in younger male subjects, phenomenologically resembles idiopathic dystonia, so can take the form of torticollis or axial dystonia for example. However, retrocollis, or opisthotonic trunk movements, are more common than in idiopathic torticollis or axial dystonia, as are so-called 'copulatory' pelvic thrusting movements. Tardive dystonia can often be functionally, as well as socially disabling. The remission rate for this condition is very low – only 14% even 8 years after discontinuation of the offending drug, which nevertheless remains the best prognostic feature.

Although the newer 'atypical' neuroleptic drugs appear to be safer with regard to the provocation of tardive movement disorders than older drugs, there are no entirely safe dopamine receptor blocking drugs and, at least for tardive dystonia, no safe period of use. Unfortunately, centrally acting dopamine receptor blocking drugs continue to be used inappropriately for depression and anxiety and also for gastrointestinal disorders such as nausea or vomiting (e.g. metoclopramide).

Anticholinergics can worsen choreiform tardive dyskinesia, but may improve tardive dystonia. Tetrabenazine can sometimes help both. Paradoxically, just as tardive dyskinesia can present when the offending neuroleptic drug has its dose reduced, or is discontinued, an increase in the dose of the offending drug can improve the movements, but only in the short term, before further aggravating the problem.

Tardive tics, myoclonus and tremor have been described, but are very uncommon.

The neuroleptic malignant syndrome (NMS) is a potentially fatal reaction to the introduction, increase or change of dosage of dopamine receptor blocking drugs (Chapter 19). In its fully developed form it involves the subacute appearance of severe muscle rigidity (sometimes with necrosis and myoglobinuria, leading to renal failure), akinesia, diaphoresis, agitation progressing to stupor and coma, and hyperpyrexia. CPK levels are elevated, often markedly, and a polymorphonuclear leucocytosis is common. Management includes stopping the offending drug, intensive care, cooling, antipyretics, and traditionally the administration of dantrolene and bromocriptine. Mortality in severe cases can still be up to 20%, but is much less in milder cases. The underlying mechanism is thought to be a combination of hypothalamic and striatal dopamine receptor blockade. Rarely an NMS-like syndrome can occur in PD after acute reduction or withdrawal of dopaminergic drugs.

Restless legs syndrome

Restless legs syndrome (RLS) is probably the most common movement disorder, affecting to some degree 3–10% of the population, with most of those needing treatment being over the age of 50 years. It causes unpleasant sensations or an urge to move in the legs (and sometimes other body parts), classically on retiring to bed at night, which is only, and almost instantly, relieved by getting up and walking about. It can also occur when trying to relax when sitting or lying down during the day. Some (younger onset) cases are dominantly inherited. There are associations with iron deficiency, uraemia, pregnancy, peripheral neuropathy and possibly with PD. Serum ferritin is often low (Chapter 19).

Essential criteria for diagnosis are as follows:

1 An urge to move the legs, usually accompanied by uncomfortable or unpleasant sensations in the legs.
2 These symptoms begin or worsen during periods of rest or inactivity such as lying or sitting.
3 Symptoms are partially or totally relieved by movement, at least for as long as the activity continues.
4 Symptoms are worse, or only occur, in the evening or at night.

Supportive criteria are as follow:

1 Positive response to dopaminergic treatment;
2 Periodic limb movements during wakefulness or sleep; and
3 Positive family history suggestive of autosomal dominant inheritance.

If drug treatment is needed, dopamine agonists (e.g. pramipexole and ropinirole) are currently favoured over levodopa because chronic levodopa treatment can lead to 'augmentation' – i.e. spillover of symptoms to the daytime, an increase in severity of symptoms, and involvement of other body parts. Second line drugs that sometimes help are opiates, gabapentin, carbamazepine and clonazepam. If there is iron deficiency or low ferritin, iron supplementation is indicated.

RLS is commonly associated with periodic leg movements of sleep (PLMS). Several gene associations for RLS (with or without PLMS) and for PLMS (with or without RLS) have recently been discovered.

Painful legs and moving toes

This rare condition is characterized by slow undulating flexion–extension movements of the toes, accompanied by pain in the legs, usually unilateral. There may be evidence of peripheral nerve or root lesion involving the affected leg. No treatment is effective.

Stiff person syndrome, stiff limb syndrome and encephalomyelitis with rigidity

Stiff person syndrome is characterized by axial rigidity at rest involving mainly trunk (causing hyperlordosis) and sometimes also proximal lower limb muscles. A crucial finding is the presence of continuous motor unit activity in the paraspinal muscles that persists even when trying to relax, so that EMG electrical silence cannot be obtained. The rigidity and continuous motor unit activity lessen, or even disappear, during sleep and after spinal or general anaesthesia, indicating a central source.

Exteroceptive or cutaneo-muscular reflexes are enhanced, habituate poorly and spread as reflex spasms into muscles normally not involved in the reflex. These findings point to enhanced spinal interneurone excitability, caused by defects either within spinal interneuronal networks at a segmental level or their descending control. Polysynaptic reflexes are characteristically exaggerated in both upper and lower limbs as well as the axial (paraspinal) muscles.

Most patients have anti-GAD antibodies in serum and CSF, and some have additional diabetes or other autoimmune disturbances or markers. Typically, patients show a useful response to high-dose baclofen and diazepam, and remain ambulant.

The stiff limb syndrome is rarer, and characterized by rigidity, painful spasms and abnormal postures of (usually one) distal limb (more commonly a leg than an arm). Affected patients show continuous motor unit activity in the affected limb, abnormal exteroceptive reflexes and abnormally segmented EMG activity during spasms. Auto-immune markers are infrequent, and the condition responds poorly to treatment, most patients becoming wheelchair-bound.

A third, even rarer, disorder comprises patients with a rapidly progressive and fatal inflammatory encephalomyelitis with rigidity, usually with abnormal CSF and additional denervation.

Neurophysiological assessment of movement disorders

Neurophysiological investigations in movement disorders are objective methods to investigate and support clinical diagnosis of different abnormal movements, and to monitor their severity and the effects of treatment.

Many methods are available, most of them useful for research purposes, but often of limited clinical utility. All electrophysiological tests should be interpreted in conjunction with clinical features but neurophysiology may disclose information that it is not possible to obtain by clinical observation alone.

Tremor

Tremor is the movement disorder most subjected to neurophysiological study. It can be characterized on the basis of its frequency, pattern of muscle activation, and duration and amplitude of the muscle bursts. Multichannel EMG recording and accelerometer data can be very useful to assess freqency and other characteristics of muscle activation in tremor.

The situation in which tremor occurs (rest, postural, action), and the presence of associated neurological signs, are important to guide the electrophysiological diagnosis of tremor. Tremor frequency can be helpful to some degree. Thus, the upper limit of frequency of physiological or voluntary tremor in healthy subjects is 11 Hz. Tremor above this frequency is always pathological, and most commonly caused by orthostatic tremor with a frequency of 13–18 Hz. Tremor at 5–7 Hz is often seen in patients with PD and essential tremor (ET) and tremor at >9 Hz in patients with enhanced physiological tremor (EPT). Low frequency tremor <4 Hz may be seen in Holmes tremor, dystonic tremor and cerebellar tremor. However, there is considerable overlap in frequency between different tremor disorders. Tremor amplitude is of little value for diagnostic purposes.

Tremor can arise from different sources. External loading (500–1000 g in the hand) typically reduces the tremor frequency in peripheral tremor (physiological tremor, EPT), but not in central tremor (PD, ET).

Cortical tremor (rhythmic cortical myoclonus) may show burst duration as short as 25–50 ms. Otherwise, burst duration is not particularly useful in identifying the anatomical origin of a tremor. Multichannel EMG recording may show a rostro-caudal pyramidal progression of the pattern of muscle recruitment, or rhythmic arrests of muscle tone as in negative cortical myoclonus or asterixis. The pattern of muscle activation between agonist and antagonist muscles (synchronous versus alternating) is not very helpful in guiding the diagnosis.

Dystonic tremor is an irregular tremor usually below 7 Hz. It is associated with dystonic postures in the affected extremity or elsewhere, is subject to position- and task-specific worsening, and increases with attempts to move the body part in the opposite direction to the dystonic pattern.

In psychogenic tremor, amplitude often diminishes and frequency may change during distraction (counting, or tapping with the opposite limb). Furthermore, tapping different frequencies with the unaffected hand 'entrains' to the same frequency as that on the tremulous side. Tremor amplitude and frequency usually increase when adding a load to the affected limb.

Dystonia

Many neurophysiological abnormalities have been found in patients with dystonia, but these are only partially useful for diagnostic purposes in individual patients. Impaired reciprocal inhibition of forearm flexor muscles at intermediate and long latency, reduced cortical silent period duration, and short- and long-interval intracortical inhibition have been seen in different studies in dystonic patients.

More sophisticated analyses of EMG discharges consider EMG–EMG coherence. This may disclose the character of the descending discharges responsible for the abnormal muscle activity in dystonia. An abnormal 4–7 Hz drive is seen in dystonic muscles in patients with the *DYT1* gene mutation, idiopathic torticollis and myoclonus dystonia. In the arms there is evidence of an abnormal cortico-muscular drive in the 15–30 Hz band leading to co-contraction between antagonistic muscles, with the exception of writer's cramp where a discrete peak in EMG–EMG coherence may be seen at 11–12 Hz.

Myoclonus

Myoclonus is classified according to its physiopathological basis as cortical, reticular or spinal.

Cortical myoclonus

This is usually arrhythmic but can also be rhythmic (cortical tremor). It is characterized by jerks of short duration (typically <50 ms) involving many muscles and usually synchronously in agonists and antagonists. EMG recording from an extremity can demonstrate spread of jerks from the proximal muscle to distal with velocity corresponding to that of alpha motor fibres.

In cortical myoclonus, the EEG often shows multifocal or generalized spike and wave or multiple spike and wave which is usually time-locked to the muscle jerks. However, in some cases the EEG does not show any time-locked abnormality. EEG back-averaging can disclose myoclonus-related EEG activity that may not be recognized on the conventional polygraph. This technique can determine the precise time interval from the EEG activity to the myoclonus. It also identifies the scalp distribution of the myoclonus-related EEG activity based on simultaneous multichannel recordings. Back-averaging analysis shows a positive–negative biphasic spike at the central electrode somatotopically representing the muscle from which the myoclonus is recorded. The initial positive precedes the onset of myoclonic EMG discharge in a hand muscle by approximately 20 ms. The more distal the muscle the myoclonus is recorded from, the longer is the EEG–EMG time interval. Myoclonus-related discharge spreads through the motor cortex within one hemisphere, and also transcallosally to the homologous area of the contralateral motor cortex (10–15 ms). Unfortunately, EEG back-averaging analysis is limited by muscle activity in the scalp and also in cases where the jerks are of high frequency, or are infrequent.

In subjects in whom myoclonic EMG bursts are of small amplitude, or repeat rhythmically at high frequency, frequency analysis has advantages over back-averaging. Frequency analysis of EMG–EMG and also EEG–EMG coherence can detect a pathologically exaggerated common drive in distal limb muscles, showing significant coherence in the physiological range (15–60 Hz) but also, in some cases, at much higher frequencies.

Patients with cortical myoclonus may also show giant sensory evoked potentials; the initial components, a post-central negative peak (N20) and a precentral positive peak (P20), are not enhanced; however, the subsequent components (P25, P30, N35) are 3–10 times as large as normal. Long loop reflexes (C-reflexes) obtained by the motor subthreshold stimulation of the median nerve, recording from both thenar muscles, are also enhanced with a latency in the thenar muscle of around 45 ms, and 10–15 ms longer contralaterally because of the transcallosal transit time. Negative myoclonus is produced by a sudden (50–400 ms) interruption of a tonic muscle contraction, associated with an ictal discharge.

In CJD, myoclonus is not stimulus-sensitive and occurs continuously and quasi-periodically in the resting condition every 600–1500 ms. There may be accompanying dystonic posturing. EMG bursts are similar to, or slightly longer than, those of classic cortical myoclonus. Periodic sharp discharges (PSDs) are usually associated with muscle jerks, but can occur independently. EEG spike-wave and EMG activity correlate loosely. On back-averaging, the negative spike-wave is much smaller than the PSD recorded with raw EEG. The time interval between EEG and jerks is 50–85 ms (much longer than required for conduction through the pyramidal tract). Typical cortical reflex myoclonus may be seen in late stages of disease.

In subacute sclerosing panencephalitis (SSPE) sudden movements, followed by a tonic phase ('hung-up jerks'), can be related to periodic high-amplitude EEG discharges occurring every 4–13 s.

Essential myoclonus, myoclonus dystonia (except for SSPE), palatal and oculo-palatal myoclonus are characterized by EMG discharges lasting up to 400 ms. In such cases the EEG does not show any specific correlate to the EMG discharge.

Reticular, or brainstem, myoclonus

This is characterized by generalized jerks with prominent involvement of proximal and flexor muscles. Jerks may be spontaneous or stimulus-induced, particularly with respect to sound.

Jerks originate from the brainstem reticular formation; the first muscle to be activated is trapezius or sternomastoid; subsequently there is spread to the cranial and caudal muscles with different velocities of activation.

Myoclonic jerks may be associated with cortical spikes. However, the lack of correlation between the two suggests that spikes are projected to, but do not originate at the cortex. Evoked potentials are not increased, but there may be an enhanced C-reflex.

The normal human startle response consists of a brief flexion response, most marked in the upper half of the body, elicited by unexpected auditory, and sometimes somaesthetic, visual or vestibular stimuli. Conduction of efferent impulses both upwards and downwards from the generator, possibly in the medial reticular formation, is slow. The shortest latencies are 20–50 ms for the orbicularis oculi muscle. In the quadriceps muscle the latencies of the responses are 100–150 ms.

Electromyographic responses in the intrinsic hand and foot muscles are particularly delayed. However, the auditory startle reflex electromyographic latencies are rather variable. The constant reflex EMG activity in orbicularis oculi is the most important event in the normal auditory startle reflex. If one considers the auditory blink reflex in orbicularis oculi as separate from the startle response, then the earliest muscle recorded is the SCM, with a latency of <100 ms. The activity then spreads up the brainstem from the XIth nerve to the Vth cranial nerve and down the spinal cord (reflex brainstem myoclonus). In physiological startle the stimulus-induced response tends to habituate, and disappears after 4–6 stimuli. Exaggerated startle responses are seen in hyperekplexia, in neuropsychiatric startle syndrome and in stimulus-induced epilepsy and stiff person syndrome.

Spinal myoclonus

Two different patterns of spinal myoclonus are recognized: proprio-spinal myoclonus and segmental myoclonus. Myoclonus is most often positive, but negative myoclonus may also occur.

Proprio-spinal myoclonus is characterized by arrhythmic sequences or runs of axial jerks producing flexion or extension of the trunk. Bursts of muscle activity vary from 50 ms to 4 s. EMG jerks arise from abdominal or cervical spinal segments and slowly spread rostrally and caudally at <10 m/s. Cranial muscles are not involved, with the exception of the neck. It can be stimulus-sensitive.

Segmental myoclonus is described as regular or irregular repetitive jerks, involving a group of muscles innervated by one or two spinal segments.

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6

Epilepsy and Related Disorders

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Epilepsy is a common condition. It accounts for about 20% of all neurological consultations and is associated with significant medical, social and secondary handicap. The World Health Organization (WHO) has estimated that epilepsy causes 6.4 million disability-adjusted life years (DALYs) and 1.32 million years of life (YLL) lost worldwide, and amongst neurological diseases is less only than stroke and dementia in its impact.

A standard definition of epilepsy is as a disorder of brain characterized by an ongoing liability to recurrent epileptic seizures. An epileptic seizure is defined as the transient clinical manifestations that result from an episode of epileptic neuronal activity. The epileptic neuronal activity is a specific dysfunction, characterized by abnormal synchronization, excessive excitation and/or inadequate inhibition, and can affect small or large neuronal populations. The clinical manifestations are sudden and usually brief. They include motor, psychic, autonomic and sensory phenomenon, with or without alteration in consciousness or awareness, and the symptoms depend on the part of the brain involved in the epileptic neuronal discharge, and the intensity of the discharge.

Epidemiology

The incidence of epilepsy is in the region of 80 cases per 100,000 persons per year, with different studies showing rates varying mostly between 50 and 120 per 100,000 per year. Its point prevalence has been found to be 4–10 cases per 1000 persons in most studies, although higher figures are found from settings in resource-poor countries. The frequency of epilepsy is also slightly higher in lower socio-economic classes. The incidence of seizures is age dependent, with the highest rates in the first year of life and a second peak in late life. About 40% of patients develop epilepsy below the age of 16 years of age and about 20% over the age of 65 years.

An isolated (first and only) seizure occurs in about 20 persons per 100,000 each year. The cumulative incidence of epilepsy – the risk of an individual developing epilepsy in his/her lifetime – is 3–5%. The fact that prevalence is much lower than cumulative incidence demonstrates that in many cases epilepsy remits. In fact, the prognosis is generally good, and within 5 years of the onset of seizures 50–60% of patients will have entered long remission. However, in about 20% of cases, epilepsy, once developed, never remits. Fertility rates are reduced by about 30% in women with epilepsy. Standardized mortality rates are also 2–3 times higher in patients with epilepsy than in others in the population. The excess mortality is caused largely by the underlying cause of the epilepsy. However, some deaths are directly related to seizures and there are higher rates of accidents, sudden unexpected death and suicides amongst patients with epilepsy when compared with the general population. The rates of death are highest in the first few years after diagnosis – reflecting the underlying cerebral disease (e.g. tumour, stroke). In chronic epilepsy, the excess mortality is partly a result of sudden unexpected death in epilepsy (SUDEP). The rates of SUDEP range from about 1 death per 2500 persons per year in mild epilepsy to 1 death per 100 patients per year amongst those with severe and intractable epilepsy.

About 30% of children with epilepsy and 20% of adults with epilepsy have additional learning or neurological disabilities. Epilepsy occurs in about 20% of those with learning disability. Of adults with newly diagnosed epilepsy, 18% show additional cognitive impairment and 6% motor disabilities (usually hemiplegia due to stroke) and 6% severe psychiatric disorders. About 1 in 15 persons with epilepsy is dependant on others for daily living because of epilepsy and the associated handicaps.

ILAE classification of seizure type

The International League Against Epilepsy (ILAE) classification of seizure type is the most widely accepted classification scheme for epilepsy. It has undergone a series of revisions since it was first

Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

Table 6.1 The International League Against Epilepsy (ILAE) Classification of Seizure Type (1981).

I. Partial (focal, local) seizures

A. Simple partial seizures
1. With motor signs
2. With somatosensory or special sensory symptoms
3. With autonomic symptoms or signs
4. With psychic symptoms

B. Complex partial seizures
1. Simple partial onset followed by impairment of consciousness
2. With impairment of consciousness at onset

***C. Partial seizures evolving to secondarily generalized seizures* (tonic–clonic, tonic, or clonic)**
1. Simple partial seizures evolving to generalized seizures
2. Complex partial seizures evolving to generalized seizures
3. Simple partial seizures evolving to complex partial seizures evolving to generalized seizures

II. Generalized seizures (convulsive and non-convulsive)

A. Absence seizures
1. Absence seizures
2. Atypical absence seizures

B. Myoclonic seizures

C. Clonic seizures

D. Tonic seizures

E. Tonic–clonic seizures

F. Atonic seizures

III. Unclassified epileptic seizures

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proposed and further revisions are under consideration. The current classification divides seizures into generalized and partial categories (Table 6.1). Generalized seizures are those that arise from large areas of cortex in both hemispheres, in which consciousness is always lost, and are subdivided into seven categories. Partial seizures are those that arise in specific often small loci of cortex in one hemisphere. They are divided into simple partial seizures which occur without alteration of consciousness and complex partial seizures in which consciousness is impaired or lost. A secondarily generalized seizure has a partial onset (the aura) which spreads to become a generalized attack. Simple partial seizures may spread to become complex partial seizures, and either can spread to become secondarily generalized. The classification is based entirely on clinical and electroencephalography (EEG) phenomenology, but some generalized seizure types occur only in specific types of epilepsy. Partial seizures invariably imply focal brain pathology, although this may not necessarily be demonstrated by conventional clinical investigation. About two-thirds of newly diagnosed epilepsies are partial and/or secondarily generalized.

Partial seizures

Simple partial seizures

These are defined as partial seizures in which consciousness is not impaired. Complex partial seizures are those in which consciousness is impaired. Both imply focal cerebral disease and seizures can arise from any cortical region, the most common sites being the frontal and temporal lobes.

The symptomatology depends on the anatomical localization of the seizures. Motor manifestations can include jerking, spasm or posturing, speech arrest, dysarthria, choking sensations, version of the head or eyes or, less commonly, rotation of the whole body can occur in epilepsy arising in many cortical areas. Todd's paralysis can occur after a seizure, and is a reliable lateralizing sign of epilepsy arising in contralateral motor cortex. Sensory manifestations can take the form of tingling or numbness or pain. Visual phenomena such as flashing lights and colours occur if the calcarine cortex is affected. A rising epigastric sensation is the most common manifestation of a simple partial seizure arising in the mesial temporal lobe. Autonomic symptoms occur such as changes in skin colour, blood pressure, heart rate, pupil size and piloerection.

Complex perceptual or affective 'auras' can take various forms, and are more common in complex partial than in simple partial seizures. They can occur in epilepsy arising from temporal, frontal or parietal foci. There are six principal categories:

1 *Dysphasic symptoms* can occur if cortical speech areas (frontal or temporoparietal) are affected and should be distinguished where possible from anarthria (speech arrest) which suggests a fronto-central origin.

2 *Dysmnestic symptoms* (disturbance of memory) such as flashbacks, déjà vu, jamais vu, or distortions of memory are most common in mesial temporal lobe seizures although also occur in inferior frontal or lateral temporal lobe seizures.

3 *Cognitive symptoms* include dreamy states and sensations of unreality or depersonalization and occur primarily in temporal lobe seizures.

4 *Affective symptoms* include fear (the most common symptom), depression, anger, elation, erotic thoughts, serenity or exhilaration. These are encountered most common in mesial temporal lobe epilepsy. Laughter (without mirth) is a feature of the automatism of seizures (known as gelastic seizures) which arise in frontal areas, and are a consistent feature of the epilepsy associated with hypothalamic hamartomas.

5 *Illusions* of size (macropsia, micropsia), shape, weight, distance or sound are usually features of temporal or parieto-occipital epileptic foci.

6 *Structured hallucinations* of visual, auditory, gustatory or olfactory forms, which can be crude or elaborate, are usually caused by epileptic discharges in the temporal or parieto-occipital association areas. Hallucinations of taste, usually an unpleasant taste, are a frequent symptom of temporal lobe epilepsy. Visual hallucinations can vary greatly in sophistication from simple colours or flashing lights in epilepsy arising in calcerine cortex to complex visual perceptual hallucinations in posterior temporal association areas. Auditory hallucinations and changes in auditory perception also vary in complexity, and most commonly occur in seizures arising in Herschl's gyrus.

Complex partial seizures

These arise from the temporal lobe in about 60% of cases, the frontal lobe in about 30% and from other cortical areas in about 10% of cases. The clinical features reflect the site of onset of the seizures. The complex partial seizure may evolve during its course and in some seizures it is possible to identify three distinct components: the aura, the absence (loss of consciousness) and the automatism. The aura is in effect a simple partial seizure. It is usually short-lived, lasting a few seconds or so, although in rare cases can be prolonged. Many patients experience isolated auras as well as full-blown complex partial seizures. The symptoms in the aura can take any of the forms described above and depend on the anatomical location of the epileptic discharge. Absence is characterized by motor and speech arrest, during which the patient appears vacant (the 'motionless stare').

Automatisms are defined as involuntary motor actions that occur during or in the aftermath of epileptic seizures, in a state of impaired awareness. The patient is usually totally amnesic for the events of the automatism. Sometimes the actions have purposeful elements, are affected by environment and can involve quite complex activity. Automatisms should be distinguished from post-ictal confusion. Automatisms are most common in temporal and frontal lobe seizures. The most common automatisms are as follow:

- *Oro-alimentary automatisms* in which orofacial movements occur such as chewing, lip smacking, swallowing or drooling. These are characteristic of partial seizures of mesial temporal origin.
- *Gestural automatisms* include fiddling movements with the hands, tapping, patting or rubbing, ordering and tidying movements. Complex actions such as undressing are quite common also as are genitally directed actions. These too are most common in mesial temporal lobe epilepsy.
- *Ambulatory automatisms* involve walking, circling, running and are most common in frontal lobe epilepsy, but do occur in temporal lobe epilepsy also.
- *Verbal automatisms* include words and sentences, meaningless sounds, humming and whistling. Speech during the seizure suggests a non-dominant focus and dysphasia after the seizure a dominant focus. Verbal automatisms can occur in both frontal and temporal seizures.
- *Violent behaviour* can occur in an automatism, is best considered as a response in an acutely confused person and is especially likely if the patient is restrained. The violent actions of the epileptic automatism are generally never premeditated, never remembered, never highly coordinated or skilful and seldom goal-directed; these are useful diagnostic features in a forensic context.

Partial (focal) epilepsy can also be classified by anatomical location. This is a phenomenological classification, based largely on the clinical and EEG appearances of the seizures, and is obviously important when considering surgical therapy. The most common schemes divide seizures into those arising in frontal, temporal, parietal and occipital lobes and also in the central region (pre- and post-central gyrus). Subdivisions are proposed, but because epileptic seizure discharges spread extensively, anatomical classifications are often not as specific as might be hoped. Sixty per cent of partial epilepsies arise in the temporal lobe (Table 6.2).

Partial seizures may spread to become generalized. The partial seizure is often experienced as an aura in the seconds before the generalized seizure. The generalized seizure is usually tonic–clonic, tonic or atonic.

The EEG during a complex partial seizure of mesial temporal lobe onset typically shows, at the onset, a rhythmic (5–7 Hz) discharge localized to the anterior mid temporal lobe. In lateral temporal seizures, the ictal onset EEG changes are more likely to have a spiked or high-frequency pattern. Complex partial seizures of frontal lobe epilepsy show ictal EEG onset patterns that are typically generalized or widespread, comprising high-frequency activity or slow rhythms or attenuation. Ictal onset EEG patterns in parietal and occipital seizures vary, in part dependent on pathways of seizure propagation, and there is a higher rate of false localization and lateralization.

Generalized seizures

Six forms are defined in the ILAE classification although, in practice, transitional forms or manifestations modified by therapy are common. Consciousness is impaired from the onset of the attack, motor changes are bilateral and more or less symmetric, and the EEG patterns are bilateral and grossly synchronous and symmetrical over both hemispheres.

Typical absence seizure (petit mal seizure)

The seizure takes the form of an abrupt sudden loss of consciousness (the absence) and cessation of all motor activity. Tone is usually preserved, and there is no fall. The patient is not in contact with the environment, inaccessible and often appears glazed or vacant. The attack ends as abruptly as it started, and previous activity is resumed as if nothing had happened and there is no post-ictal confusion. The patient is often unaware that an attack has occurred. Most absence seizures (>80%) last less than 10 seconds. Blinking, subtle clonic movements, alterations in tone and/or brief automatisms can occur, particularly in longer attacks. The attacks can be repeated, sometimes hundreds of times a day, often cluster and are often worse when the patient is awakening or drifting off to sleep. Absences may be precipitated by fatigue, drowsiness, relaxation, photic stimulation or hyperventilation. Typical absence seizures develop in childhood or adolescence and are encountered almost exclusively in the syndrome of idiopathic generalized epilepsy. The EEG during a typical absence is diagnostic, shown high voltage, regular, symmetric and synchronous 3 Hz spike-wave paroxysms. The features useful in differentiating a complex partial seizure and a typical absence are shown in Table 6.3.

Table 6.2 Partial seizures arising in different brain regions.

Brain region of origin	Clinical features
Mesial temporal lobe origin	Tripartite seizure pattern (aura, absence, automatism), although only one feature may be present Auras are common and include: visceral, cephalic, gustatory, dysmnestic, affective, perceptual or autonomic auras Partial awareness commonly preserved, especially in early stages Slow evolution of seizure Prominent motor arrest or absence (the 'motionless stare') Dystonic posturing of the contralateral upper limb common in the early stages of the seizure In seizures arising in the dominant temporal lobe, speech arrest common during the seizures and dysphasia common post-ictally Seizures longer than frontal lobe seizures (typically >2 min), with a slower evolution and more gradual onset/offset Post-ictal confusion and dysphasia common Autonomic changes (e.g. pallor, redness, and tachycardia) Automatisms: less violent than in frontal lobe epilepsy, and usually take the form of oro-alimentary (lip smacking, chewing, swallowing), or gestural (e.g. fumbling, fidgeting, repetitive motor actions, undressing, walking, sexually directed actions, walking, running) and sometimes prolonged In hippocampal epilepsy, history of febrile seizures, onset in childhood or adolescence, initial early response lost after several years
Lateral temporal lobe onset	Features overlap with mesial temporal lobe onset, with the following differences: Motor arrest and absence less prominent Aura more likely to take the form of complex perceptual changes, visual and auditory hallucinations Tonic posturing more common More frequent secondary generalization
Frontal lobe origin	Frequent attacks with clustering Brief stereotyped seizures (<30 s) Nocturnal attacks common Sudden onset and cessation, with rapid evolution and awareness lost at onset Absence of complex aura Version of head or eye common Prominent ictal posturing and tonic spasms Prominent complex bilateral motor automatisms involving lower limbs; often bizarre and misdiagnosed as pseudoseizures Absence of postictal confusion Frequent secondary generalization History of status epilepticus
Parietal and occipital lobe origin	Somatosensory symptoms (e.g. tingling, numbness or more complex sensations – may or may not march) Sensation of inability to move Sexual sensations Illusions of change in body size/shape Vertigo Gustatory seizures Elementary visual hallucinations (e.g. flashes, colours, shapes, patterns) Complex visual hallucinations (e.g. objects, scenes, autoscopia palinopsia, often moving) Head turning (usually adversive, with sensation of following or looking at the visual hallucations) Visuo-spatial distortions (e.g. of size (micropsia, macropsia), shape, position) Loss or dulling of vision (amaurosis) Eyelid fluttering/blinking/nystagmus
Central cortical origin	Often no loss of consciousness Contralateral jerking (which may or may not march) Contralateral tonic spasm or dystonia Posturing, which is often bilateral Speech arrest and paralysis of bulbar musculature (producing anarthria or a choking, gurgling sound) Contralateral sensory symptoms Short duration and frequently recurring attacks Prolonged seizures with slow progression (and episodes of epilepsia partialis continua) Post-ictal Todd's pareisis

Table 6.3 Differentiation between typical absences and complex partial seizures.

	Typical absence	Complex partial seizure
Age of onset	Childhood or early adult	Any age
Aetiology	Idiopathic generalized epilepsy	Any focal pathology or cryptogenic epilepsies
Underlying focal anatomical lesion	None	Limbic structures Neocortex
Duration of attack	Short (usually <30 s)	Longer, usually several minutes
Other clinical features	Slight (tone changes or motor phenomena)	Can be prominent; including aura, automatism
Postictal	None	Confusion, headache, emotional disturbance are common
Frequency	May be numerous	Usually less frequent cluster
Ictal and interictal EEG	3 Hz generalized spike-wave	Variable focal disturbance
Photosensitivity	10–30%	None
Effect of hyperventilation	Often marked increase	None, modest increase

Table 6.4 Clinical features differentiating typical and atypical absence seizures.

	Typical absence	Atypical absence
Context	Otherwise no neurological signs or symptoms	Usually in context of learning difficulty, and other neurological abnormalities
Consciousnes	Totally lost	Often only partially impaired
Focal signs in seizures	Nil	May be present
Onset/offset of seizures	Abrupt	Often gradual
Coexisting seizure types	Sometimes tonic–clonic and myoclonic	Mixed seizure disorder common, all seizure types

Atypical absence seizure

This, like typical absence seizures, takes the form of loss of awareness (absence) and hypo-motor behaviour (Table 6.4). However, the duration is longer, loss of awareness is often incomplete and much less marked and associated tone changes are more severe than in typical absence seizures. The onset and cessation of the attacks are not so abrupt. Amnesia may not be complete and the subject may be partially responsive. The ictal EEG shows usually diffuse but often asymmetric and irregular spike-wave bursts at 2–2.5 Hz, and sometimes fast activity or bursts of spikes and sharp waves. The background interictal EEG is usually abnormal, with continuous slowing, spikes or irregular spike-wave activity, and there is overlap of ictal and interictal EEG features. Atypical absences occur in the symptomatic epilepsies, are usually associated with learning disability, other neurologic abnormalities or multiple seizure types. These seizures most commonly form part of the Lennox–Gastaut syndrome and occur at any age.

Myoclonic seizure

This takes the form of a brief contraction of a muscle, muscle group or several muscle groups brought about by a cortical discharge. It can be single or repetitive, varying in severity from an almost imperceptible twitch to a severe jerking, resulting, for instance, in a sudden fall or the propulsion of handheld objects. Recovery is immediate, and the patient often maintains that consciousness was not lost. Myoclonic seizures occur in idiopathic generalized epilepsy, in the childhood epileptic encephalopathies (e.g. Lennox–Gastaut syndrome) and in epilepsy associated with other forms of learning disability, and in the progressive myoclonic epilepsies. Focal myoclonus can also occur in focal epilepsy of frontal or occipital origin. Epileptic myoclonus needs to be differentiated from non-epileptic myoclonus of spinal and subcortical origin.

Clonic seizure

Clonic seizures are most frequent in neonates, infants or young children, and are always symptomatic.

Tonic seizure

This takes the form of a tonic muscle contraction with altered consciousness without a clonic phase. Often there is extension of the neck; contraction of the facial muscles, with the eyes opening widely, upturning of the eyeballs, contraction of the muscles of respiration, spasm of the proximal upper limb muscles causing the abduction and elevation of the semi-flexed arms and the shoulders. The ictal EEG may show flattening (desynchronization), fast activity (15–25 Hz) with increasing amplitude (to about 100 μV) as the attack progresses, or a rhythmic 10 Hz discharge similar to that seen in the tonic phase of the tonic–clonic seizure. Tonic seizures occur in the setting of diffuse cerebral damage, learning disability, are invariably associated with other seizure types and are the characteristic and defining seizure type in the Lennox–Gastaut syndrome.

Tonic–clonic seizure (grand mal seizure)

This is the 'convulsion' or 'fit'. It is sometimes preceded by a prodromal period during which an attack is anticipated, often by an ill-defined vague feeling or sometimes more specifically, for instance, by the occurrence of increasing myoclonic jerking. If an aura then occurs (in fact a simple or complex partial seizure) in the seconds before the full-blown attack, this indicates that the tonic–clonic seizure is secondarily generalized. The seizure takes the form of loss of consciousness, sometimes with the epileptic cry (a loud guttural sound), tonic stiffening (and the patient will fall if standing) initially sometimes in flexion but then in axial extension, with the eyes rolled up, the jaw clamped shut, the limbs stiff, adducted and extended, and the fists clenched. Respiration ceases and cyanosis is common. The eyes remain open and the pupils dilated and unreactive. There are frequently heart rate changes, which are sometimes marked and can take the form of tachycardia or bradycardia and even asystole. This tonic stage lasts on average 10–30 seconds and is followed by the clonic phase, during which convulsive movements, usually of all four limbs, jaw, and facial muscles occur; breathing can be stertorous and arrest of respiration can occur; and saliva (sometimes blood-stained owing to tongue biting) may froth from the mouth. The convulsive movements decrease in frequency (eventually to about four clonic jerks per second), and increase in amplitude as the attack progresses. The attack is usually followed by a period of flaccidity of the muscles and consciousness is slowly regained. Confusion is invariable in the post-ictal phase. The patient often has a severe headache, feels dazed and extremely unwell, and often lapses into deep sleep. Petechial haemorrhages around the eyes, lethargy and muscle aching is common. Tonic–clonic seizures are encountered in many different types of epilepsy, including idiopathic generalized epilepsy, symptomatic generalized epilepsies, epileptic encephalopathies, in various epilepsy syndromes, in febrile convulsions and in acute symptomatic seizures. They have no pathological or syndromic specificity.

Atonic seizure

The most severe form is the classic drop attack (astatic seizure) in which all postural tone is suddenly lost causing collapse to the ground like a rag doll. The seizures are short and are followed by immediate recovery. Longer (inhibitory) atonic attacks can develop in a stepwise fashion with progressively increasing nodding, sagging or folding. The seizures are always associated with diffuse cerebral damage, learning diability and are common in severe symptomatic epilepsies (especially in the Lennox–Gastaut sndrome and in myoclonic astatic epilepsy).

ILAE classification of the epilepsies and epilepsy syndromes

An epileptic syndrome is defined as 'an epileptic disorder characterized by a cluster of signs and symptoms customarily occurring together', and the ILAE classification scheme attempts to categorize epilepsy according to syndrome (Table 6.5). Some

Table 6.5 The International League Against Epilepsy (ILAE) classification of the epilepsies and epilepsy syndromes (1989).

1. Generalized

- Idiopathic generalized epilepsies with age-related onset (in order of age)
  - Benign neonatal familial convulsions
  - Benign neonatal convulsions
  - Benign myoclonic epilepsy in infancy
  - Childhood absence epilepsy
  - Juvenile absence epilepsy
  - Juvenile myoclonic epilepsy
  - Epilepsy with generalized tonic–clonic seizures on awakening
  - Other generalized idiopathic epilepsys not defined above
  - Epilepsies with seizures precipitated by specific modes of activation
- Cryptogenic or symptomatic generalized epilepsies (in order of age)
  - West's syndrome
  - Lennox–Gastaut syndrome
  - Epilepsy with myoclonic astatic seizures
  - Epilepsy with myoclonic absences
- Symptomatic generalized epilepsies
  - Non-specific aetiology
    - Early myoclonic encephalopathies
    - Early infantile encephalopathy with burst suppression
    - Other symptomatic epilepsies not defined above
  - Specific syndromes
  - Epilepsies in other disease states

2. Localization-related epilepsies

- Idiopathic with age-related onset
  - Benign epilepsy with centrotemporal spikes
  - Childhood epilepsy with occipital paroxysms
  - Primary reading epilepsy
- Symptomatic
  - Epilepsia partialis continua
  - Syndromes characterized by specific modes of precipitation
  - Temporal lobe epilepsies
  - Frontal lobe epilepsies
  - Parietal lobe epilepsies
  - Occipital lobe epilepsies
- Idiopathic

3. Epilepsies and syndromes undetermined as to whether focal or generalized

- With both generalized and focal seizures
  - Neonatal seizures
  - Severe myoclonic epilepsy in infancy
  - Electrical status epilepticus in slow-wave sleep
  - Acquired epileptic aphasia
- Other undetermined epilepsies (not defined above) with unequivocal generalized or focal features

4. Special syndromes

- Febrile convulsions
- Isolated seizures or isolated status epilepticus
- Seizures occurring only when there is an acute metabolic or toxic event due to factors such as alcohol, drugs, eclampsia, non-ketotic hyperglycinaemia

syndromes have single aetiologies and specific features, but others have multiple causes and heterogenous clinical features. The syndromes are often age specific, and over time in individual patients one epileptic syndrome can evolve into another (e.g. West's syndrome commonly evolves into Lennox–Gastaut syndrome). The same seizure type can occur in very different syndromes (e.g. myoclonic seizures in the benign syndrome of juvenile myoclonic epilepsy and the refractory syndromes of the progressive myoclonic epilepsies). The classification scheme allows a more comprehensive approach to categorization than simply classifying by seizure type, but is not widely used in routine clinical practice.

The following are the most common syndromes.

Idiopathic generalized epilepsy

This term should be used to denote a common and important category of epilepsy that has a characteristic clinical and electrographic pattern and a presumed genetic basis. Idiopathic generalized epilepsy (IGE) accounts for about 10–20% of all patients with epilepsy. There is probably usually a polygenic basis, but no common susceptibility genes have yet been found.

The condition is sometimes subdivided into separate syndromes, although this is contentious and there is a great deal of overlap. The core clinical features shared to a greater or lesser extent by these syndromes (at least those with onset in later childhood or early adult life) and the common subdivisions are shown in Table 6.6. The most important subdivisions are:

Childhood absence epilepsy

This condition, more common in girls, appears in childhood (peak age 6–7 years), and is not associated with learning disability or other neurological problems. It accounts for 1–3% of newly diagnosed epilepsies and up to 10% of childhood epilepsies. The seizures take the form of generalized absence attacks. These comprise an abrupt sudden loss of consciousness and the cessation of all motor activity. Tone is preserved, and there is no fall. The patient is not in contact with the environment, and appears glazed or vacant. The attack ends as abruptly as it started, and previous activity is resumed as if nothing had happened. There is no confusion and the patient is often unaware that an attack has occurred. Sometimes there is blinking, slight clonic movements, partial loss of tone and/or brief automatisms. The attacks can cluster and can be very frequent (sometimes hundreds of times a day) and are precipitated by fatigue, drowsiness, relaxation, photic stimulation or hyperventilation. The classic EEG pattern is a regular 3-Hz spike-wave. About one-third of patients also develop generalized tonic–clonic seizures. The prognosis is good, and rapid remission on therapy is expected in 80% or more of patients. When followed up after age 18 years, only approximately 20% of previously diagnosed patients are still having seizures.

Table 6.6 Subdivisions of idiopathic generalized epilepsy.

Epilepsy with myoclonic absences
Childhood absence epilepsy
Juvenile absence epilepsy
Juvenile myoclonic epilepsy
Epilepsy with grand mal seizures on awakening
Absence epilepsy with peri-oral myoclonus

Juvenile myoclonic epilepsy

This is the most common subtype of IGE, and accounts for up to 10% of all epilepsies. The characteristic seizures are brief myoclonic jerks, occurring in the first hour or so after awakening, and usually in bursts. These are sudden, shock-like jerks, affecting mainly the shoulders and arms, usually but not always symmetrically. It is often not clear whether consciousness was retained or lost. In 80% of cases, the myoclonus develops between the ages of 12 and 18 years. In about 80% of cases, generalized tonic–clonic seizures also occur, usually months or years after the onset of myoclonus, and it is these that often trigger the diagnosis. About one-third of patients also develop typical absence seizures, again usually on awakening. About 5% of patients exhibit strong photosensitivity. The myoclonic seizures (and other seizures) can be precipitated by photic stimuli, lack of sleep, alcohol, hypoglycaemia and poor compliance with medication. Complete response to treatment can be expected in 80–90% of cases, but lifelong therapy may be needed.

Epilepsy with grand mal seizures on awakening

This condition overlaps considerably with other generalized epilepsies especially with juvenile myoclonic epilepsy in which most affected people also have generalized tonic–clonic seizures (GTCS) on awakening. The EEG usually has a normal background with bursts of generalized spike-waves or polyspike-waves. Whether this syndrome represents a discrete entity or simply part of the spectrum of other forms of IGE has been the subject of discussion for several decades, without clear resolution.

Benign partial epilepsy syndromes

There are a number of benign partial epilepsy syndromes. As with the IGEs, there is overlap between syndromes and the subdivision is a matter of some contention.

Benign partial epilepsy with centrotemporal spikes

This condition (BECTS; *syn*: rolandic epilepsy, benign epilepsy with rolandic spikes) is the most common 'idiopathic' partial epilepsy syndrome, accounting for perhaps 15% of all epilepsies. The peak age of onset is 5–8 years and over 80% of cases have onset at 4–10 years. The condition reflects an age-related genetically determined neuronal hyperexcitability in the rolandic area. The characteristic EEG feature is the high-amplitude rolandic spike, and 10% of children with the EEG disturbance do not actually have seizures. The seizures are infrequent, and 50% of children experience a total of less than five attacks in all. Fifty per cent of seizures occur only at night, and the daytime seizures usually occur when the child is tired or bored. The complex partial seizures take a characteristic form, usually beginning with spasm and clonic jerking of one side of the face and throat muscles, then speech arrest and guttural vocalizations. The seizures may evolve to secondarily generalized tonic–clonic attacks. There are no associated neurological disturbances and intellect is normal. The epilepsy ceases in almost all cases, usually by the age of 12 years, without long-term sequalae. There is an excellent response to therapy with carbamazepine or other antiepileptic drugs. The condition is usually quite benign although some children have associated learning difficulties and the characteristics of more severe cases merge into other more severe childhood epileptic syndromes.

Early onset benign occipital epilepsy (*syn*: Panayiotopoulos syndrome)

This syndrome occurs between 1 and 14 years (mean 4–5 years). The partial seizures take the form of eye deviation, nausea and vomiting, with subsequent evolution into clonic hemiconvulsions. Typically, the seizures are prolonged, often lasting hours and are infrequent (mean number three). The interictal EEG shows occipital spikes, with a morphology similar to that in BECTS, often continuous and abolished by eye opening (the fixation-off phenomenon). However, it is misleading to consider these as 'occipital lobe' seizures and the spikes may reflect spread. Some seizures consist only of vomiting, of syncopal symptoms or prominent autonomic symptoms. The prognosis is uniformly excellent, and the epilepsy always remits over time without adverse sequaelae. This syndrome is often misdiagnosed as migraine.

West syndrome

West syndrome has an incidence of 0.25–0.42/1000 live births. It is defined by the occurrence of infantile spasms and the EEG changes of hypsarrhythmia. The infantile spasms take the form of sudden, generally bilateral and symmetrical contractions of the muscles of the neck, trunk or limbs, tend to cluster and may occur hundreds of times a day. In the most common type, the flexor muscles are predominantly affected, and the attack takes the form of sudden flexion with arms and legs held in adduction (the so-called salaam attacks). The peak age of onset is 4–6 months and 90% develop in the first year of life. Most cases have an underlying cerebral developmental pathology. The most common cause is tuberous sclerosis (7–25% of all cases); neonatal ischaemia and infections (about 15% of all cases); lissencephaly and pachygyria and hemimegalencephaly (about 10% of cases); Down syndrome and acquired brain insults. The prognosis is poor, with most cases developing severe epilepsy, intellectual and psychomotor deterioration. About 5% of children die in the acute phase of spasms.

Lennox–Gastaut syndrome

This term is used to denote an age-specific epileptic encephalopathy with a characteristic clinical seizure and EEG pattern and learning disability. However, whether it is a specific syndrome or whether the symptoms and EEG changes simply reflect severe childhood epilepsy with learning disability is a source of contention. There are many potential underlying causes and there is no specific histopathological change nor specific treatment. About 1–5% of childhood epilepsies conform to this pattern. The age of onset is between 1 and 7 years and it can develop in patients who earlier had West syndrome, myoclonic astatic epilepsy or neonatal seizures. In one-third of cases no cause is identifiable (cryptogenic Lennox–Gastaut syndrome). About one-third of cases are caused by malformations of brain development. The epilepsy is very severe, with seizures usually occurring many times a day. These take the form of atypical absence, tonic, myoclonic, tonic and tonic–clonic seizures, and later complex partial and other seizure types develop. The most characteristic are tonic attacks, which occur most often in non-REM (but not REM) sleep and in wakefulness. Non-convulsive status (atypical absence status) may last hours or days and be repeated on an almost daily basis. The EEG shows a characteristic pattern with the presence interictally of long bursts of diffuse slow (1–2.5 Hz) spike-wave activity, widespread in both hemispheres, roughly bilaterally synchronous but often asymmetrical. The background activity is abnormal with an excess of slow activity and diminished arousal or sleep potentials. Learning disability is the other major feature of the condition. At least 50% of cases have an intelligence quotient (IQ) below 50. The prognosis for control of seizures and for the development of intellectual impairment is poor, and many patients require institutional care in childhood and in adult life, and are dependent for daily activities. Response to treatment is often poor, and the seizure disorder can be exacerbated by over treatment or therapy with sedating drugs. Carbamazepine and benzodiazepines may exacerbate tonic or atonic seizures.

Febrile seizures

Febrile seizures are seizures that occur in the context of an acute rise in body temperature in children between 3 months and 5 years of age, in whom there is no evidence of intracranial infection or other defined cause. About 3–5% of children will have at least one attack, and 19–41/1000 infants with fever will convulse. The first febrile seizure happens in the second year of life in 50%. In over 85%, the seizures are generalized and are usually brief. The seizure usually occurs early in the febrile illness, and in about one-quarter of cases is the first recognizable sign of the illness. These essentially benign seizures need to be differentiated from the 5–10% of first seizures with fever in which the seizure is in fact caused by viral or bacterial meningitis, and from other cases where the fever lights up an existing latent predisposition to epilepsy. About 35% of susceptible children will have a second febrile seizure and 15% three or more. Recurrence is more common if the initial convulsion was at a young age, in those in whom the convulsion occurred at a relatively low temperature and in those with prolonged initial convulsions. In about 10–20% of children, subsequent neurodevelopment problems are noted, but these usually reflect pre-existing problems and are not brought about by the convulsions. About 2–10% of children with febrile seizures will later develop epilepsy. The risk is higher in those with pre-existing neurodevelopmental dysfunction. It has been proposed that febrile convulsions can sometimes cause hippocampal sclerosis, and by this mechanism subsequent temporal lobe epilepsy, particularly if the febrile convulsion was prolonged or severe; how frequently this occurs is unknown.

Causes of epilepsy

Epilepsy is often a multifactorial condition, and even if there is a predominant cause, genetic and environmental factors often play a part in its clinical manifestations. The range of causes differs in different age groups, patient groups and geographical locations. Broadly speaking, genetic, congenital and perinatal conditions are the most common causes of early childhood onset epilepsy, whereas in adult life, epilepsy is more likely to be result from external non-genetic causes, but this distinction is by no means absolute. In late adult life vascular disease is increasingly common. In certain parts of the world, endemic infections such as malaria or cysticercosis are common causes. The approximate frequencies of different aetiologies in a typical Western population are shown in Table 6.7.

Idiopathic epilepsy (epilepsy resulting from genetic or developmental causes)

The 'idiopathic' epilepsies are likely to have a strong genetic basis, usually polygenic or oligogenic in nature, and their expression is often age dependent. Single gene disorders probably underlie only 1–2% of all epilepsies, and usually in these conditions there are additional neurological or systemic features.

Pure epilepsies resulting from single gene disorder

There is a small number of rare conditions in which epilepsy is the main or only manifestation that is Mendelian in its inheritance pattern. These include benign familial neonatal convulsions which start in the first 10 days of life and which usually remit spontaneously, although 10% of patients develop subsequent epilepsy. This is an autosomal dominant condition resulting from mutations of voltage-gated potassium channel genes *KCNQ2* and *KCNQ3*.

Table 6.7 Causes of epilepsy and approximate frequency.

Cause	Frequency (%)*
Idiopathic (?oligogenic)	10–30
Vascular	10–20
Congenital	5–10
Neurodegenerative/other neurological conditions	5–10
Hippocampal sclerosis	5–10
Neoplasm	5–10
Trauma	5
Childhood epilepsy syndrome	5
Infection/metabolic/toxic	3–5
Genetic (single gene disorder)	1–2
Unknown/cryptogenic	25–30

*Approximate prevalent frequency in Western population.

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is another condition brought about by mutations in the α_4 and β_2 subunits of the nicotinic acetylcholine receptor. In this condition, purely nocturnal frontal lobe complex partial seizures occur, sometimes each night. The seizures are brief, lasting less than 1 minute, and are clustered around the onset and end of sleep. The seizures can be misdiagnosed as parasomnias or even pseudoseizures (in spite of the fact that pseudoseizures never arise from sleep), and are not uncommonly resistant to therapy.

Generalized epilepsy with febrile seizures (GEFS+) is a more heterogeneous form of epilepsy, inherited in an autosomal dominant fashion, with age-specific manifestations and variable penetrance. Febrile seizures are the most constant feature, in which seizures are precipitated by fever and tend to occur throughout childhood, but other afebrile seizures also occur. The phenotype is wide and it is arguable whether this condition really deserves to be called a syndrome. Various mutations underlying the epilepsy in these families have been identified in the α or β subunits of the voltage-gated sodium channel genes *SCN1A* and *SCN1B*, and γ_2 subunit of the $GABA_a$ receptor.

Dravet syndrome (severe myoclonic epilepsy of infancy [SMEI]) is a severe epilepsy, developing in early life and with a poor prognosis. Most cases have mutations in the *SCNIA* gene, the same gene that causes the more benign GEFS+, and indeed there are families in which both phenotypes coexist. Seizures occur between the ages of 2 and 9 months, and are often prolonged clonic or tonic–clonic seizures, and are precipitated by fever or even hot baths. Myoclonic seizures develop later and episodes of non-convulsive status epilepticus are common. The prognosis is poor with intractable epilepsy, early death, severe retardation or institutionalization in all cases.

Pure epilepsies with complex (presumed polygenic) inheritance

These are much more common than the single gene epilepsies. These are divided into idiopathic generalized epilepsies and benign partial epilepsies of childhood. Although presumed to be genetic, no common susceptibility genes have yet been identified. To what extent other cryptogenic epilepsies have a genetic basis is less clear (e.g. febrile convulsions, cryptogenic West's syndrome, cryptogenic Lennox–Gastaut syndrome). These conditions are probably best conceptualized as polygenic disorders in which the phenotype is the result of interactions between susceptibility genes and environmental effects. There is often no strong family history and genetic studies have to be conducted using case control methodology in large populations.

Epilepsies in other single gene disorders

At least 240 single gene and chromosomal disorders result in neurological disorders in which epilepsy is part of the phenotype. Most are rare or very rare, and manifest initially in childhood (Table 6.8).

Table 6.8 Some single-gene disorders causing epilepsy.

Agenesis of the corpus callosum
Acute intermittent porphyria
Angelman's disease
Arginino-succinicaciduria
Carnitine palmitoyltransferase 11 deficiency
Chorea-acanthocytosis (neuro-acanthocytosis)
DRPLA
Familial cavernoma
Glucocerebrosidase deficiency (Gaucher disease)
Hexosaminindase A deficiency
Huntington's disease
Isovaleric acidaemia
Lafora body disease
Maple syrup urine disease
Menkes disease
Methylmalonic aciduria
Mitochondrial diseases (MERFF, MELAS, Leigh syndrome)
Mucopolysaccharidoses
Neuronal ceroid lipofuscinoses
Niemann–Pick disease
Ornithine trans-carbamylase deficiency
Peri-ventricular heterotopia
Peroxisomal enzyme deficiencies
Phenylalanine hydroxylase deficiency (phenylketonuria)
Pyridoxine deficiency
Pyruvate dehydrogenase deficiency
Rett's syndrome
Sialidoses
Tuberous sclerosis
Unverricht–Lundborg disease
Urea cycle disorders
Wolf–Hirshhorn syndrome
Zellweger's syndrome

List excludes the single gene disorders causing 'pure epilepsy' – see text.
DRPLA, dentato-rubro-pallido-luysian atrophy; MERFF, myoclonic epilepsy with ragged red fibres; MELAS, Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke.

Table 6.9 Causes of progressive myoclonic epilepsy (PME).

Most common causes
Baltic myoclonus (Unverricht–Lundborg disease)
Ceroid lipofuscinoses
DRPLA
Lafora body disease
Mitochondrial disease (MERRF)
Sialidoses

Rarer causes
Alper's disease
Alzheimer's disease
Biotin-responsive progressive myoclonus
Coeliac disease
Gaucher's disease
GM2 gangliosidosis (juvenile type)
Hexosaminidase deficiency
Huntington's disease
Juvenile neuroaxonal dystrophy
Menkes disease
Non-ketotic hyperglycinaemia
Phenylketonuria
Tetrahydrobiopterin deficiencies

In a significant proportion of patients, no cause can be identified.
DRPLA, dentato-rubro-pallido-luysian atrophy; MERFF, myoclonic epilepsy with ragged red fibres.

Progressive myoclonic epilepsy

This form of epilepsy can be caused by various genetically determined neurological disorders (Table 6.9). In most parts of the world, the four most common are: mitochondrial diseases, Unverricht–Lundborg disease, dentato-rubro-pallido-luysian atrophy (DRPLA) and Lafora body disease.

Unverricht–Lundborg disease (Baltic myoclonus) is the most benign form. It is an autosomal recessive disorder resulting from dodecamer repeats in the *EPM1* gene coding for the cystatin B protein, a protease inhibitor. The condition is particularly common in Finland (where the incidence is in excess of 1/20,000 persons) and other Scandinavian countries as a result of founder effects. Myoclonus develops, usually between the ages of 6–15 years, and the condition slowly progresses. Ataxia and tremor later become major clinical features. There is a very slow intellectual decline.

DRPLA is inherited in an autosomal dominant fashion. It is particularly common in Japan (a frequency of 0.2–0.7/100,000 persons) and northern Europe. It is a triplet repeat disorder involving the *DRPLA* gene which is of uncertain function. The condition presents in childhood or adult life and is slowly progressive. Ataxia, choreoathetosis, dementia and behavioural changes, myoclonus and epilepsy occur.

Lafora body disease is an autosomal recessive condition, most common in southern Europe, and characterized by Lafora bodies, periodic acid–Schiff (PAS) positive intracellular polyglucosan inclusions found in neurones, sweat glands and elsewhere. The age of onset is 6–19 years and patients develop progressive myoclonic, tonic–clonic and partial seizures. There is also a progressive and severe dementia, and ataxia and dysarthria also occur. Death occurs within 2–10 years. Up to 80% of patients have a mutation in the *EPM2A* gene, which codes for Laforin, a tyrosine phosphatase protein. A second gene, *EPM2B* has been identified, which codes for Malin, a ubiquitin ligase protein.

Mitochondrial cytopathy (myoclonic epilepsy with ragged red fibres [MERRF]) is one of the phenotypes of mitochondrial cytopathy. In 90% of cases, the genetic defect is an A–G transition at nucleotide-8344 in the tRNA^{lys} gene of mtDNA, and some other cases are caused by *T8356C* or *G8363A* mutations. This is a multi-system disorder with a very variable phenotype in which myoclonic seizures are often the first symptom, followed by generalized epilepsy, myopathy, ataxia and dementia.

Heteroplasmy is responsible for some of the phenotypic variation (Table 6.9).

Epilepsies in neurocutaneous syndromes

The neurocutaneous conditions often result in epilepsy. Tuberous sclerosis complex, Sturge–Weber syndrome and neurofibromatosis (type 1) are the most important. Other rare conditions causing epilepsy include hypomelanosis of Ito, epidermal naevus syndrome (Jadassohn's syndrome), hereditary haemorrhagic telangiectasia, midline linear naevus syndrome, incontinentia pigmenti and Klippel–Trenaunay–Weber syndrome.

Tuberous sclerosis

This is a not uncommon condition (1/5800 live births in some studies) and there is a high spontaneous mutation rate (1/25,000). It is inherited in an autosomal dominant fashion. To date, about 300 unique *TSC1* or *TSC2* mutations have been identified. The clinical features of the condition are variable. Epilepsy is the presenting symptom in 80% or more of patients. It can take the form of neonatal seizures, West's syndrome, Lennox–Gastaut syndrome or as adult onset partial or generalized seizures. About two-thirds of patients present with seizures before the age of 2 years, with motor seizures, drop attacks or infantile spasms. About 25% of all cases of West's syndrome are caused by tuberous sclerosis. The skin is abnormal in almost all patients, and skin lesions include: hypomelanotic macules (87–100% of patients), facial angiofibromas (47–90%), shagreen patches (20–80%), fibrous facial plaques and subungual fibromas (17–87%). CNS tumours are the leading cause of morbidity and mortality. The brain lesions can be distinguished on the basis of magnetic resonance imaging (MRI) studies and comprise: subependymal glial nodules (90% of cases), cortical tubers (70% of cases) and subependymal giant cell astrocytomas (6–14% of cases). Fifty per cent of patients have developmental delay or mental retardation. An estimated 80% of children with tuberous sclerosis have identifiable renal tumours by the age of 10 years. Cardiac and retinal lesions also occur.

Sturge–Weber syndrome

This is an uncommon sporadic developmental disorder, of uncertain causation. The cardinal features are a unilateral or bilateral port wine naevus, epilepsy, hemiparesis, mental impairment and ocular signs. The port wine naevus is usually but not exclusively in the distribution of the trigeminal nerve. It can cross the midline and spread into the dermatomal distribution of the upper cervical nerve. In one-third of cases the naevus is bilateral. The epilepsy can be focal or generalized. It is often the earliest symptom, and most patients with Sturge–Weber develop seizures within the first year of life (at least 70%) and almost all have developed epilepsy before the age of 4 years. Adult onset epilepsy can occur occasionally. The early seizures are often triggered by fever. The seizures take the form of partial or multi-focal attacks often with frequent and severe secondary generalization. Convulsive status occurs in over half of cases. Seizures developing in the neonatal period can be very difficult to control and carry a poor prognosis. The hemiplegia and mental impairment deteriorate in a stepwise fashion following a severe bout of seizures, and this is one of the few situations where clear-cut cerebral damage results directly from epileptic attacks, presumably by ischaemic or excitotoxic mechanisms. Severe learning disability is now less common because of better control of the epilepsy. Status epilepticus particularly often results in a permanent and significant worsening of the neurological deficit. The epilepsy should be aggressively treated to prevent neurological deterioration. Resective surgery (either lesionectomy, hemispherectomy or lobectomy) should be given early consideration.

Cortical dysplasia

Cortical dysplasia (*syn*: cortical dysgenesis, malformations of cortical development) is a term that is applied to developmental disorders of the cortex producing structural change. In most cases the cause is unknown, but a minority are caused by identifiable genetic abnormalities and others by environmental influences such as infection, trauma, hypoxia, exposure to drugs or toxins. The clinical features vary, but epilepsy and learning disability are the most common manifestations. Cortical dysplasia is the underlying cause of the epilepsy in up to 30% of children and 10% of adults referred to epilepsy centres for intractable epilepsy.

Hemimegalencephaly

In this condition, one cerebral hemisphere is enlarged and is structurally abnormal with thickened cortex, reduced sulcation and poor or absent laminar organization. Giant neurones are found throughout the brain and in 50% of cases balloon cells too. The condition can occur in isolation, associated with other cortical dysplasias or as part of other syndromes (notably tuberous sclerosis or other rarer neurocutaneous syndromes). Hemimegalencephaly results in severe epilepsy with learning disability, hemiplegia and hemianopia. Surgical therapy (hemispherectomy or hemispherotomy) can be curative.

Focal cortical dysplasia

There are a variety of subtypes, with different histological appearances caused possibly by formation at different stages of embryogenesis. In some the cortical lamination is normal, but in others there may be associated widespread macrogyria and polymicrogyria. Epilepsy is the leading symptom, and other features depend on the extent of the lesion and include learning disability and focal deficits.

Schizencephaly

This term denotes the presence of clefts in the cortex, stretching from the surface to the ventricle. Schizencephaly can be unilateral or bilateral and is often peri-sylvian in location. The causes are heterogeneous, and include germline mutations of the homeobox gene *EMX2* and environmental insults during development including radiation, infection and ischaemia. Epilepsy is the most common symptom (over 90% of cases), associated usually but by no means always with learning disability or cognitive changes.

Focal neurological deficit is common in extensive or bilateral cases.

Agyria pachygyria band spectrum (lissencephaly, pachygyria, agyria and subcortical band heterotopia)

These abnormalities of cortical gyration are grouped together as they show an interconnected genetic basis. In all the gyration is simplified and the cortex is thickened. Lissencephaly (literally, smooth brain) is the most severe form, in which gyration is grossly diminished or even absent. Subcortical band heterotopia (*syn*: double cortex syndrome) denotes the presence of a band of grey matter sandwiched by white matter below the cortical grey matter. The band may be thin or thick, and can merge with overlying cortex in which case the cortex takes a macrogryic form. It is caused in about 80% of cases by germline deletions in the DCX (*XLIS*) gene and occurs almost always (but not exclusively) in females. The pachygyria and bands are anteriorly predominant. The genetic anomaly in the other 20% of cases has not been identified.

Macrogyria refers to thickened cortex, and can occur as an isolated phenomenon, is variable in extent and when focal is indistinguishable on clinical or imaging grounds from some forms of focal cortical dysplasia. Isolated lissencephaly is present in 12 per million live births and results in profound retardation, epilepsy and spastic quadrapareisis. In less severe cases, where the lissencephaly is restricted to one region of the brain (albeit usually bilaterally, with an anterior or posterior gradient), the epilepsy and learning disability may be mild. Of cases of isolated lissencephaly, 60–80% are caused by identifiable mutations in the *LIS1* or *XLIS* (also known as the DCX) genes, on 17p13.3 and Xq22.3-q24, respectively, and in 40% the entire gene is deleted. Other forms of lissencephaly have more widespread associations. The best known is the Miller–Dieker syndrome, caused by large deletions of *LIS1* and of several other contiguous genes on 17p13.3, in which the lissencephaly is associated with epilepsy, facial dysmorphism, microcephaly, small mandible, failure to thrive, retarded motor development, dysphagia, decorticate and decerebrate postures. All these conditions usually present in children with epilepsy and learning disability. The clinical severity of the syndrome seems to correlate with the extent of the cerebral anomaly.

Agenesis of the corpus callosum

This anomaly occurs in various genetic and congenital disorders. Epilepsy is invariable and is the leading symptom. In Aicardi's syndrome, the corpus callosum agenesis is associated with periventricular heterotopia, thin unlayered cortex and diffuse polymicrogyria.

Polymicrogyria

The appearance of small and prominent gyri, separated by shallow sulci, is known as polymicrogyria. It can have a genetic or environmental cause. Epilepsy is the leading clinical feature, associated with learning disability and focal neurological signs and the manifestations vary greatly in severity. Bilateral peri-sylvian polymicrogyria (Kuzniecky syndrome) is a condition in which there is severe upper motor neurone bulbar dysfunction and diplegia as well as severe epilepsy and mental retardation.

Peri-ventricular nodular heterotopia (syn: bilateral peri-ventricular nodular heterotopia, subependymal nodular heterotopia)

In this condition, subependymal nodules of grey matter are present, usually bilateral and located along the supralateral walls of the lateral ventricles. It is much more common in females, inherited in an X-linked dominant fashion and almost all cases have shown mutations in the *FLN1* (filamin-1) gene. The clinical presentation can vary from mild epilepsy presenting in older children or young adults to severe infantile or childhood partial epilepsy.

Symptomatic epilepsy (epilepsy resulting from acquired causes)

Almost any condition affecting the cerebral grey matter can result in epilepsy. The epilepsy usually takes a partial or secondarily generalized form and, in most causative conditions, the epilepsy does not have any particularly distinctive features. After an acute cerebral event, the epilepsy is often divided into 'early' (i.e. seizures occurring within a week of the insult) and 'late' (i.e. chronic epilepsy developing later). There is often a 'silent period' between the injury and the onset of late epilepsy, and the nature of the epileptogenic process occurring during this period is largely unknown. The occurrence of a silent period raises the possibility that neuroprotective interventions to inhibit these processes could prevent later epilepsy, but to date no effective neuroprotectant agent is available. Antiepileptic drug therapy will prevent early epilepsy but does not reduce the frequency of late seizures. Early seizures are often not followed by late epilepsy – a fact important to emphasize to patients.

Hippocampal sclerosis

Hippocampal sclerosis is the most common cause of mesial temporal lobe epilepsy which is itself the most common form of partial epilepsy. It is found in over one-third of patients with refractory focal epilepsy attending hospital clinics in whom there is no other structural lesion, but is less frequent in those with mild epilepsy. Hippocampal sclerosis typically causes complex partial seizures of mesial temporal origin. There is a clear association with a history of childhood febrile convulsions, and it has been proposed that the febrile convulsions, especially if prolonged or complex, results in hippocampal sclerosis which itself results in subsequent temporal lobe epilepsy. Serial MRI studies have demonstrated that status epilepticus also can result in hippocampal sclerosis and there is clear evidence from animal experimentation that prolonged partial seizures can cause hippocampal damage and in some cases progression of the hippocampal atrophy and worsening seizures. In other cases, hippocampal sclerosis may be a congenital lesion, and hippocampal sclerosis can also occur after severe brain trauma or vascular damage.

Cerebral palsy, perinatal and prenatal injury

Cerebral palsy is a non-specific term that covers many prenatal and perinatal pathologies. It is strongly associated with epilepsy. In the US National Collaborative Perinatal Project, a prospective cohort study of infants followed to the age of 7 years, epilepsy was found to occur in 34% of children with cerebral palsy, and cerebral palsy was present in 19% of children developing epilepsy. In the same cohort, the risk of learning disability (associated with cerebral palsy) was 5.5 times higher among children developing epilepsy following a febrile seizure than in children with a febrile seizure alone. Learning disability (IQ <70) is present in 27% of children with epilepsy, and seizures are present in about 50% of children with mental retardation and cerebral palsy. In controlled studies, only severe perinatal insults have been found to increase the risk of subsequent epilepsy, e.g. perinatal haemorrhage, ischaemic hypoxic encephalopathy. Factors such as pre-eclampsia, eclampsia, forceps delivery, being born with the 'cord round the neck', low birth weight or prematurity have only a very modest association, if any, with subsequent epilepsy.

Post-vaccination encephalopathy

The possible role of vaccination (particularly pertussis vaccination) in causing a childhood encephalopathy and subsequent epilepsy and learning diability has been the subject of intense study, with contradictory claims. The UK National Childhood Encephalopathy Study found that children hospitalized with seizures and encephalopathy were more likely to have received DTP (diptheria, tetanus, pertussis) vaccination in the previous 7 days than control children. However, the potential methodological bias of this study has been severely criticized. A more recent large series of 368,000 children after immunization, found no difference in rates of epilepsy when compared with controls. Similarly, suggestions that MMR (mumps, measles, rubella) vaccine increases the risks of autism and epilepsy are now thought to be unfounded. A recent study has shown that many cases of so-called post-vaccination encephalopathy have in fact the causal mutation of SMEI and so the vaccination was in all likelihood a non-causal factor in the development of the encephalopathy. Conventional medical advice is now that vaccination is safe, and although a small number of children do develop encephalopathic reactions that result in later epilepsy, this number is considerably less than the risk of encephalopathy after the naturally occurring viral illnesses that vaccination prevents. The vaccines that have been thought to be associated with post-vaccination encephalomyelitis are smallpox, measles, DTP, Japanese B encephalitis and rabies.

Cerebral tumour

About 6% of all newly diagnosed cases of epilepsy are caused by cerebral tumours. The incidence of tumour is higher in adults than in children. Seizures occur in about 50% of all brain tumours. Tumours of the frontal and temporal regions are more likely to cause epilepsy than other cortical tumours and epilepsy is rare in subcortical or cerebellar tumours.

Gliomas are most common brain tumour causing epilepsy, and low grade gliomas are more epileptogenic than high-grade tumours. Overall, slow-growing or benign tumours account for about 10% of all adult epilepsies. There can be a history of epilepsy for many years. In chronic refractory tumoural epilepsy, oligodendrogliomas account for 10–30%, dysembryoplastic neuroepithelial tumours (DNETs) for 10–30%, astrocytomas for 10–30%, gangliogliomas for about 10–20% and hamartomas for 10–20%. The epilepsy derives from the surrounding tissue (and this can have implications for surgical therapy). Epileptogenesis can be caused by impaired vascularization of the surrounding cortex, changes in the excitatory and inhibitory synapisis or other morphological changes.

Ganglioglioma are mixed developmental tumours that are composed of neoplastic glial and neuronal cell types and comprise 10% of more of the neoplasms removed at temporal lobectomy. Seizures are the primary presenting symptom in 80–90%. The dysembryoplastic neuroepithelial tumour (DNET or DNT) is a pathological entity only recently differentiated from other forms of 'benign gliomas' and account for 10–30% of resected tumours in the temporal lobe. They are benign tumours with only a slight propensity for growth, and epilepsy is usually the only clinical symptom. As these are developmental in origin, they have instrinsic epileptogenesis (in contrast to other cerebral tumours) and are important to identify as partial resection will often control the seizures. Hamartomas are benign tumours which account for 15–20% of tumours removed at temporal lobectomy. These are more common in children.

The hypothalamic hamartoma is a particular form of hamartoma. These are benign tumours, usually confined to the tuber cinereum. They characteristically present with gelastic seizures, learning disability, behavioural disturbance and later with precocious puberty. The lesions are subtle and can be very easily missed on even high-quality MRI scanning. Gelastic seizures are characteristic of hypothalamic hamartoma but do occur in other midline lesions and also occasionally in temporal lobe epilepsy. The attacks take the form of sudden laughter associated with other variable motor features (clonic movements, head and eye deviation). The laughter is 'mirthless', is not associated with any emotional feelings of joy or happiness and occurs in situations that do not provoke humour.

Meningiomas are also common causes of adult epilepsy, and epilepsy is the presenting symptom of the tumour in 20–50% of cases. Meningiomas were more likely to cause epilepsy when located over the convexity, parasagittal/falx and sphenoid ridge meningiomas, and with evidence of peri-tumoural oedema. There is no relationship between the presence of epilepsy and histological type.

Cerebrovascular disease

Stroke is the most commonly identified cause of epilepsy presenting over the age of 50 years, and occult stroke also explains the occurrence of other apparently cryptogenic late onset epilepsy. A history of stroke has been found to be associated with an increased lifetime occurrence of epilepsy (OR 3.3; 95% CI 1.3–8.5).

About 5–10% of patients with cerebral haemorrhage develop epilepsy. The incidence of early epilepsy (seizures in the first week) is higher, up to 30% in some series and about one-third of those with early seizures continue to have a liability to epilepsy. Epilepsy is more common after large haemorrhages and haemorrhages that involve the cerebral cortex and almost always develops within 2 years of the haemorrhage. After cerebral infarction, epilepsy occurs in about 6% of patients within 12 months and 11% within 5 years of the stroke. Epilepsy is more common in cerebral infarcts located in the anterior hemisphere, and involving cortex. Epilepsy can also complicate occult cerebrovascular disease. Late onset epilepsy can be the first manifestation of cerebrovascular disease, and in the absence of other causes, newly developing seizures after the age of 40 years should prompt a screen for vascular risk factors.

Arteriovenous malformation

An arteriovenous malformation (AVM) is a congenital malformation comprising a network of arterial and venous channels communicating directly with each other. Between 17% and 36% of supratentorial AVMs present with seizures, with or without associated neurological deficits, and 40–50% with haemorrhage. Smaller AVMs (<3 cm diameter) are more likely to present with haemorrhage than large ones. Conversely, large and/or superficial malformations are more epileptogenic, as are AVMs in the temporal lobe. About 40% of patients with large AVMs have epilepsy, and epilepsy is the presenting symptom in about 20%. The annual risk of bleeding of an AVM is in the region of 2–4% per year, irrespective of whether the malformation presented with haemorrhage, and the average mortality about 1% per year. Venous malformations are congenital anomalies of normal venous drainage and these have a very low risk of haemorrhage or epilepsy.

Cavernous haemangioma (cavernoma)

Cavernous haemangiomas account for 5–13% of vascular malformations of the CNS. At least 15–20% of patients remain symptom-free throughout their lives. Patients present with seizures (40–70%), focal neurological deficits (35–50%), nonspecific headaches (10–30%) and cerebral hemorrhage. The seizures are typically partial in nature and often brief, infrequent and minor in form. Family histories can be found in about 10–30% of cavernous haemangiomas, and three different genes (or loci) have been identified.

Other vascular lesions

Cortical venous infarcts are particularly epileptogenic, at least in the acute phase, and may underlie a significant proportion of apparently spontaneous epileptic seizures complicating other medical conditions and pregnancy for instance. Seizures occur in several connective tissue disorders and in patients with cerebral vasculitis. The most commonly encountered is systemic lupus erythematosus. Seizures also occur with cerebrovascular lesions secondary to rheumatic heart disease, endocarditis, mitral valve prolapse, cardiac tumours and cardiac arrhythmia, or after carotid endarcterectomy. Epilepsy is also common in eclampsia, hypertensive encephalopathy and malignant hypertension and in the annoxic encephalopathy that follows cardiac arrest or cardiopulmonary surgery. Unruptured aneurysms can cause epilepsy especially if large and if embedded in the temporal lobe.

Dementia and degenerative disorders

Epilepsy is a common feature of degenerative neurological disease that involves the grey matter, but is seldom a leading symptom in pure leucodystrophy.

The most common neurodegenerative disorders are the dementias in late life. Six per cent of persons over the age of 65 years have dementia, and the rate increases exponentially as a function of age. Alzheimer's disease is the most common cause of dementia, and patients with Alzheimer's disease are six times more likely to develop epilepsy than age-matched controls. Partial and secondarily generalized seizures occur, and are usually relatively easily treated with conventional antiepileptic therapy. Myoclonus is another common finding in patients with Alzheimer's disease, occurring in about 10% of autopsy-verified cases and is a late manifestation. Five percent of patients with Huntington's disease have epilepsy, usually in the later stages. Epilepsy is more common in the juvenile type, and occasionally takes the form of a progressive myoclonic epilepsy. Epilepsy, and indeed status epilepticus, can be the presenting feature of Creutzfeldt–Jakob disease. Generalized tonic–clonic or partial seizures occur in 10% of established cases, and myoclonus in 80% and can be induced by startle or other stimuli.

Post-traumatic epilepsy

Head trauma is an important cause of epilepsy. It is customary to draw a distinction between open head injury, where the dura is breached, and closed head injury, where there is no dural breach. Post-traumatic seizures are traditionally subdivided into immediate, early and late categories. Immediate seizures are defined as those that occur within the first 24 hours after injury, early seizures are those that occur within the first week and late seizures occur after 1 week.

Closed head injuries are most common in civilian practice, usually from road traffic accidents, falls or recreational injuries, and in different series have accounted for 2–12% of all cases of epilepsy. Traumatic brain injury in the USA has been estimated to have an incidence of 825 cases per 100,000 per year, with about 100–200 per 100,000 per year admitted to hospital. Early seizures after closed head injury occur in about 2–6% of those admitted to hospital, with a higher frequency in children than in adults. If mild injury is included, early seizures indicate a more severe injury, but have not been found generally to be an independent predictive risk factor of late seizures. Approximately 5% of patients requiring hospitalization for closed head trauma will subsequently develop epilepsy (late post-traumatic seizures; although estimates have varied between 2% and 25%). Mild head injury – defined as head injury without skull fracture and with less than 30 minutes of post-traumatic amnesia – is, in most studies, not associated with any markedly increased risk of epilepsy. Moderate head injury – defined as a head injury complicated by skull fracture or post-traumatic amnesia for more than 30 minutes – is followed by epilepsy in about 1–4% of cases. Severe head injury – defined as a head injury with post-traumatic amnesia of more than 24 hours, intracranial haematoma or cerebral contusion – is followed by epilepsy, in most studies, in about 10–15% of patients. The excess risk of epilepsy is highest during the first year, with onset of epilepsy peaking 4–8 months post-injury, and diminishes during the ensuing years. Post-traumatic epilepsy is much more frequent after open head injury. This is particularly so in penetrating wartime injuries, with 30–50% of patients developing subsequent epilepsy. Overall, the risk of late epilepsy, if early epilepsy is present, is about 25% compared to 3% in patients who did not have early seizures. The risk of epilepsy after open head injury is greatest if the extent of cerebral damage was large and involved the frontal or temporal regions.

Calculations of the risk of epilepsy in various circumstances following injury have been made. The presence of a dural breach (e.g. with a depressed fracture), an intracranial haematoma and long post-traumatic amnesia (≥24 hours) have been found consistently to increase significantly the risk of subsequent epilepsy. In one series, the risk of seizures by 2 years was 27% in the presence of depressed skull fracture, 24% with subdural haematoma (and 44% if this was severe enough to need surgical evacuation), 23% with intracranial haematoma and 12% with long post-traumatic amnesia.

Antiepileptic drug therapy reduces the risk of early seizures. However, there has been controversy about the role of longer term prophylactic antiepileptic drug treatment after head trauma. Early retrospective reports suggested that such prophylactic treatment reduced the incidence of subsequent epilepsy, although none of the subsequent large-scale prospective trials showed any protective effect on late seizures. Nevertheless, it is now usual to prescribe antiepileptic drugs after severe head injury for a period of 6 months or so.

Epilepsy after neurosurgery

The risk of late postoperative seizures is greater in patients with younger age, early postoperative seizures and severe neurological deficit. The incidence of seizures varies according to the nature of the underlying disease process, its site and extent. A large retrospective study found an overall incidence of 17% for postoperative seizures in 877 consecutive patients undergoing supratentorial neurosurgery for non-traumatic conditions. The patients had no prior history of epilepsy and the minimum follow-up was 5 years. The incidence of seizures ranged from 4% in patients undergoing stereotactic procedures and ventricular drainage to 92% for patients being surgically treated for cerebral abscess. The risk of craniotomy for glioma was 19%, for intracranial haemorrhage 21% and for meningioma removal 22%. All these risks were greatly enhanced if seizures occurred pre-operatively. Among patients developing postoperative seizures, 37% did so within the first postoperative week, 77% within the first year and 92% within the first 2 years. If early seizures occurred (i.e. those occurring in the first week), 41% of patients developed late recurrent seizures.

Studies after unruptured aneurysm show an overall risk of about 14%. The risk of a middle cerebral aneurysm resulting in epilepsy is 19%, and anterior communicating aneurysms and posterior communicating aneurysms carry a risk of about 10%. If the aneurysm has bled, causing an intracranial haematoma, the incidence of epilepsy is much higher.

An overall risk of epilepsy following shunt procedures is about 10%, although this depends on the site of the shunt insertion.

It is not clear whether the prophylactic use of anticonvulsants after neurosurgical procedures is worthwhile. Currently, it is usual to prescribe prophylactic anticonvulsant drugs for several months after major supratentorial neurosurgery and then gradually to withdraw the medication unless seizures have occurred.

Bacterial or viral meningitis and encephalitis

CNS infections are a major risk factor for epilepsy. Seizures can be the presenting or the only symptom, or one component of a more diffuse cerebral disorder.

Encephalitis and meningitis result in a sevenfold increase in the rate of chronic epilepsy compared to that in the general population. The increased risk is highest during the first 5 years after infection, but remains elevated for up to 15 years. The risk is much higher after encephalitis (RR 16.2), especially herpes simplex virus 1 (HSV-1) infection, than bacterial meningitis (RR 4.2) or aseptic meningitis (RR 2.3). The incidence of severe HSV-1 encephalitis is about 1 per million persons per year, and seizures are a frequent symptom in the acute phase of severe HSV encephalitis. Most survivors are left with neurological sequelae including severe epilepsy. Epilepsy is also a leading symptom of tuberculoma. In patients presenting simply with epilepsy, it is now usual to treat with antitubercular and antiepileptic drugs (with a short course of adjunctive steroids), and to defer surgery. When medical therapy is initiated without diagnostic confirmation from a biopsy, the patient should be carefully monitored, and if the mass does not decrease in size after 8 weeks of therapy, biopsy should be reconsidered.

Pyogenic brain abscess is an uncommon but serious cause of infective epilepsy. The estimated annual incidence of brain abscess in the USA is 1/10,000 hospital admissions, and abscess surgery accounts for 0.7% of all neurosurgery operations. Brain abscess can develop in association with a contiguous suppurating process (usually otitis media, sinus disease or mastoiditis, 50%), from haematogenous spread from a distant focus (25%), as a complication of intracranial surgery (15%) and trauma (10%). Commonly isolated organisms are streptococci, including aerobic, anaerobic and microaerophilic types. *Streptococcus pneumoniae* is a rarer cause of brain abscesses, which are often the sequel to occult cerebrospinal fluid (CSF) rhinorrhoea and also to pneumococcal pneumonia in elderly patients. Enteric bacteria and *Bacteroides* are isolated in 20–40% of cases and often in mixed culture. Anaerobic organisms have become increasingly important organisms and in many instances more than a single bacterial species is recovered. Gram-negative bacilli rarely occur alone. Staphylococcal abscesses account for 10–15% of cases and are usually caused by penetrating head injury or bacteraemia secondary to endocarditis. Clostridial infections are most often post-traumatic. Rarely, *Actinomyces* or *Nocardia* are the causative agents in a brain abscess.

Parasitic diseases

Neuro-cysticercosis is the most common parasitic disease of the CNS. Epilepsy is the most common clinical manifestation and usual presenting symptom and neuro-cysticercosis a major cause of epilepsy in endemic areas in parts of Latin America, Asia and West Africa. A solitary cerebral parenchymal lesion is a common form of presentation, but lesions are often multiple. Over time, the cysts shrink progressively and then calcify or disappear completely. Seizures develop when a cyst is degenerating or around a chronic calcified lesion. Where there is a single cyst it is usual to control seizures with antiepileptic drugs and not to use anticysticercal drugs. If anticysticercal drugs are to be used, steroids need to be given in co-medication to prevent sudden rise in intracranial pressure and exacerbation of symptoms.

In endemic regions, a common clinical scenario is the occurrence of a seizure with a single enhancing lesion on CT. The differential diagnosis includes neuro-cysticercosis, tuberculosis, gliomas and other tumours, toxoplasmosis and other infective lesions. Over 90% of the lesions in India are caused by neuro-cysticercosis, and currently the usual management strategy is to screen the patient for other signs of tuberculosis and if none are present, not to give antitubercular therapy. CT is repeated in 12 weeks and if the lesion has not regressed, or has increased, a review of diagnosis including surgical biopsy is the preferred approach. Antiepileptic drugs are given.

Malaria causes a 9–11-fold (95% CI 2–18) increase in the risk of chronic epilepsy – a risk that is at least double the risk of epilepsy after complex febrile seizures.

Rasmussen's encephalitis

This is an unusual condition in which chronic inflammation develops slowly and progressively in the cortex of one cerebral hemisphere. It usually begins in childhood although rare adult onset cases are described. The inflammatory process may evolve for up to 10 years or more and the symptoms and signs are usually initially slowly progressive and then eventually stabilize. The cause of the inflammation is quite unclear, but it is presumed to be an auto-immune response, and its remarkable unihemispheric distribution is also completely unexplained. The condition presents with focal and secondarily generalized seizures which can be severe and periods of epilepsia partialis continua (EPC) are common. Associated with the seizures is commonly progressive loss of motor and cognitive skills and speech (if in the dominant hemisphere). Hemipareisis and hemianopia are common. Diagnosis is suspected on MRI scanning which shows marked unilateral and progressive unihemispheric focal atrophy. Aphasia may develop in the dominant hemisphere. Treatment is difficult. Antiepileptic drugs are usually ineffective in controlling seizures. Various attempts to suppress or modulate the immune system, in particular with corticosteroids and/or intravenous immunoglobulin (IVIg) have proved effective in some cases. Surgery to control seizures can be carried out. Large resections are needed and hemispherectomy and hemispherotomy can be strikingly effective at controlling seizures and improving behaviour and cognition.

Differential diagnosis of epilepsy

Epileptic seizures feature in many differential diagnoses of transient neurological dysfunction. There are a wide variety of epileptic seizures and syndromes, with some age-specific aspects. Patients may present with more than one dominant form of episode, so the approach taken is to consider the principal differential diagnoses of the common presenting themes. There are some differences to the common presentations and differential diagnoses in adults, infants and children and we largely confine this discussion to adult patients.

The key to making a correct diagnosis is a detailed history from the individual patient and from a reliable witness who has seen the episodes in question. In individuals attending clinics with 'first seizures', not more than 25% of patients are usually considered to have had an epileptic seizure. The most common diagnostic error is to diagnose a syncopal episode as an epileptic seizure. Undue reliance is often placed on investigations, particularly the EEG and MRI. Inappropriate weight is often given to EEG findings that are 'compatible with epilepsy'.

It is a sound aphorism that the diagnosis of epilepsy is made primarily on the history, and the role of the EEG is to assist in the subsequent classification of the type of epileptic seizures and the epilepsy syndrome. The role of MRI is not to diagnose epilepsy, but to identify any underlying structural cerebral abnormality in those with diagnosed epilepsy.

There is considerable scope for the misdiagnosis or inaccurate diagnosis of epilepsy and epilepsy syndrome, which can have very serious consequences. In tertiary referral practice it is estimated that in 26% of those with a diagnosis of refractory epilepsy the diagnosis is incorrect or inaccurate.

When taking the history it is a good tactic to first allow the individual and witnesses to give their own freehand account of the points that they consider most important and to then go through the salient points in a systematic manner. It is not uncommon that a dramatic event causes the individual to seek advice and for minor events that may have occurred for some time to have been overlooked. Such minor events may produce important diagnostic clues and so need to be specifically enquired for. For example, episodes of an epigastric rising sensation, déjà vu and premonition suggest temporal lobe focal seizures; brief blank staring spells and flurries of upper limb jerks in the first hour after waking suggest a generalized epilepsy. In contrast, a greying of vision and unsteadiness on prolonged standing, which is likened to the head rush that occurs when rising up quickly from a crouch, suggest presyncope.

In those who have had repeated episodes, a videotape recording of an episode is frequently invaluable, conveying more information that can be relayed by even the most careful witness, and has the benefit of being objective. It is not uncommon for witnesses (including carers) to relate important details incorrectly, such as which arm was stiff and extended and which was jerking. As video cameras, particularly on mobile telephones, and Internet communications become increasingly prevalent, this is becoming more of a practical proposition and it is commonplace for individuals to send video recordings into the clinic, which are often extremely helpful.

The clinical examination is usually less rewarding than the history, but is still important. In addition to determining if there are any focal neurological deficits or evidence of raised intracranial pressure, the individual's mood and mental state need to be assessed. The skin should be examined for evidence of a neurocutaneous syndrome and blood pressure checked. If an individual presents with episodes of loss of awareness or falling, a cardiac examination and checking of lying and standing blood pressure is indicated.

Epileptic seizures need to be considered in the differential diagnosis of a range of presentations (Table 6.10).

Loss of awareness

Whatever the cause, the patient may have amnesia for both the event and its exact circumstances. The three main causes are syncope, seizures and cardiac arrhythmias. Transient cerebral ischaemia caused by vascular abnormalities is less common. Microsleeps (very short daytime naps) may occur with any cause of severe sleep deprivation or disruption. Other causes of diagnostic confusion are much less common and include hypoglycaemia or other intermittent metabolic disorders, structural anomalies of the skull base affecting the brainstem, or lesions affecting the circulation of the CSF.

Table 6.10 Clinical presentations of epilepsy.

Loss of awareness
Generalized convulsive movements
Drop attacks
Transient focal motor attacks
Transient focal sensory attacks
Facial muscle and eye movements
Psychic experiences
Aggressive or vocal outbursts
Episodic phenomena in sleep
Prolonged confusional or fugue states

Syncope

Syncope is the most common cause of episodes of loss of awareness. Simple faints or vasovagal syncopal attacks can usually be related to identifiable precipitants. Most often they occur on getting up quickly or standing for prolonged periods, particularly if associated with peripheral vasodilatation (e.g. during hot stuffy weather, crowded trains or rooms, or are related to drug or alcohol use). Frightening, emotional or unpleasant scenes and painful stimuli may also be triggers, because of increased vagal activity.

There are other causes of syncope, and classification depends on terminology. Cough and micturition syncope are well recognized. Changes in intrathoracic pressure (cough syncope), impaired baroreceptors resulting from atheroma of the carotid (carotid sinus syncope), cardiac arrhythmias or autonomic disturbances may also lead to cerebral hypoperfusion and fainting. As these may not be caused by vasovagal reflex changes, the typical aura of vasovagal syncope may not be present.

Epilepsy

Several types of epileptic seizure may present with loss of awareness as the only reported feature. These include absences, complex partial, tonic or atonic seizures. Typical absences involve cessation of activity, reduced or lost awareness, eyelid blinking or twitching, and sometimes small myoclonic facial or limb jerks, or brief facial automatisms such as lip smacking or chewing. Typical absences are usually brief but often occur many times per day. There may also be isolated myoclonic jerks. Atonic seizures usually give rise to drop attacks but may appear to cause blank spells if the patient is sitting or lying down and so cannot fall. Complex partial seizures may cause loss of awareness with few if any other features. Detailed enquiry must always be made for any associated psychic or motor phenomena that may raise the possibility of a seizure disorder.

Cardiac disorders

There are often prodromal features similar to simple syncope, as well as palpitations, chest pain, shortness of breath or other features of cardiovascular insufficiency. Attacks resulting from transient complete heart block or asystole are abrupt and short with rapid loss of consciousness. Lack of cardiac output may also be caused by short episodes of ventricular tachycardia or fibrillation. Prolongation of the QT interval may lead to such events. Attacks may be preceded by palpitations, extreme fatigue or presyncopal features.

Patients with mitral valve prolapse and aortic stenosis may present with episodic loss of awareness caused by fluctuating cardiac output or associated arrhythmias. Those with aortic stenosis and hypertrophic cardiomyopathy are especially prone to present with episodes of sudden collapse with loss of awareness during exercise. A cardiological opinion should be sought if there is the possibility of cardiac dysfunction causing episodes of loss of awareness, falls or convulsions (see below). A 12-lead electrocardiogram (ECG) should be carefully inspected, particularly for evidence of prolongation of the QT interval and consideration given to prolonged ECG monitoring with an implanted ECG loop recorder.

Microsleeps

Any cause of sleep deprivation can lead to brief daytime naps, sometimes lasting for only a few seconds. Impaired quality of sleep may also be a factor. The most important is obstructive sleep apnoea, although microsleeps also occur in other sleep disorders. Microsleeps are a common problem when driving, particularly on featureless straight roads and are the cause of many road traffic accidents. There are usually clear warning signs such as the driver feeling a need to close their eyes, yawn, turn the radio volume up or open the windows. These events are of legal significance as a driver who continues to drive despite such warning signs and who causes an accident is likely to be prosecuted for dangerous driving. Narcolepsy can present with short periods of suddenly falling asleep during the day. Systematic enquiry should be made for other symptoms of the narcolepsy cataplexy syndrome, such as loss of body tone precipitated by emotion or laughter, sleep paralysis and hypnogogic hallucinations.

Panic attacks

Panic attacks usually start with feelings of fear and anxiety, associated with autonomic changes and hyperventilation. This leads to dizziness or light-headedness, orofacial and/or peripheral paraesthesia (which may be asymmetric), carpopedal spasm, twitching of the peripheries, blurred vision or nausea. Occasionally these preludes may be forgotten, and attacks present with loss of awareness. Often, but not always, there is a clear precipitant, such as a particular situation. Panic attacks are almost always longer than seizures. However, none of these features are consistent, and differentiation from epilepsy can be difficult.

Hypoglycaemia

Hypoglycaemic attacks causing loss of consciousness are extremely rare except in patients with treated diabetes mellitus. Very occasional cases may be seen caused by insulin secreting tumours. There is usually a history of events occurring if meals are delayed or missed and prodromal symptoms of anxiety, sweating and unease which improve with taking glucose.

Other neurological disorders

If a head injury causes loss of consciousness, there is amnesia. In accidental head injury, particularly road traffic accidents, it may be difficult to distinguish amnesia caused by the injury from cases in which there was a loss of consciousness that caused the accident. Isolated episodes of loss of awareness may also be caused by abuse of psychotropic drugs or other substances.

Dissociative seizures

Dissociative seizures, sometimes known as non-epileptic attack disorder (NEAD) or pseudoseizures typically gives rise to episodes of two broad types:

1 Attacks involving motor phenomena; and
2 Attacks of lying motionless.

The latter are often prolonged, continuing for several minutes or sometimes hours. Such behaviour is very rare in epileptic seizures: there will nearly always be other positive phenomena in epileptic attacks that last for more than a few minutes. In addition, attacks are often precipitated by external events or stress. Patients with dissociative seizures often have a history of abnormal illness behaviour. Dissociative seizures are much more common in females than males, and usually commence in adolescence or early adulthood (Table 6.11).

Table 6.11 Differentiation of epileptic seizures and dissociative seizures.

	Epileptic seizure	Dissociative seizures
Precipitating cause	Rare	Common, emotional and stress-related
When alone or asleep	Common	May be reported
Onset	Usually short	May be short or over several minutes
Aura	Various, usually stereotyped	Fear, panic, altered mental state
Speech	Cry, grunt at onset; muttering, words in automatisms	Semi-voluntary, often unintelligible
Movement	Atonic, tonic; if clonic, synchronous small amplitude jerks	Asynchronous flailing of limbs; pelvic thrusting; opisthotonos
Injury	Tongue biting, fall; directed violence rare	May bite tongue, cheeks, lip, hands, throw self to ground. Directed violence not uncommon
Consciousness	Complete loss in generalized tonic–clonic; may be incomplete in complex partial	Variable, often inconsistent with seizure type
Response to stimulation	None in generalized tonic–clonic; may respond in complex partial and post-ictally	Often reacts and this may terminate episode
Incontinence	Common	Sometimes
Duration	Few minutes	Few minutes, may be prolonged.

Generalized convulsive movements

Epilepsy

A generalized convulsion is generally the most readily diagnosed epileptic seizure. Classically, there is a cry, generalized stiffening of body and limbs, followed by rhythmic jerking of all four limbs, with loss of awareness, eyes staring blankly, tongue biting and urinary incontinence. The generalized convulsive movements usually last for a minute or so, and as the attack proceeds the jerking slows in frequency and increases in amplitude. There is often tachycardia, apnoea and cyanosis, and afterwards irregular breathing followed by confusion, headache and sleepiness.

Syncope with secondary jerking movements

People who faint often have myoclonic twitches of the extremities for less than 1 minute. This may be associated with limb posturing and stiffening. With prolonged cerebral hypoperfusion, as may occur if the person is held upright by well-meaning bystanders, or an aircraft seat, these may be more prominent and prolonged, and be reported as 'a convulsion'. Incontinence of urine may occur, particularly if the bladder is full and tongue biting may occur if the tongue is caught between the teeth as the individual falls to the ground.

Primary cardiac or respiratory abnormalities presenting with secondary anoxic seizures

Episodes of complete heart block or transient asystole may have syncopal features followed by collapse to the ground and secondary anoxic seizures. More commonly, there is an abrupt collapse with no warning and the person is observed to be pale and witnesses commonly remark that 'they thought the person was dead'. The attacks last for less than 1 minute, but may be followed by a prolonged period of confusion, particularly in elderly patients. There should be a low threshold for obtaining a cardiological opinion in such cases and consideration given to insertion of an implanted ECG loop recorder to identify occasional cardiac arrhythmias.

Involuntary movement disorders and other neurological conditions

There is no alteration in consciousness. The best known is paroxysmal kinesiogenic choreoathetosis. Attacks are usually precipitated by sudden specific movements and last a few seconds to minutes. Paroxysmal dystonia can present with attacks that last for minutes to hours. Patients with involuntary movement disorders such as idiopathic torsion dystonia may show severe acute exacerbations that may mimic convulsive movements.

Patients with mental retardation often have stereotyped or repetitive movements, which may include head banging or body rocking, and more subtle movements which may be difficult to differentiate from complex partial seizures.

Hyperekplexia

Hyperekplectic attacks are characterized by excessive startle, may cause stiffening and collapse with a sudden jerk of all four limbs. Attacks are provoked by sudden unexpected stimuli, most commonly auditory. Hyperekplexia needs to be distinguished from seizures induced by startle, which commonly arise from the frontal lobe.

Dissociative seizure

Dissociative seizures involving prominent motor phenomena are more common than those with arrest of activity. Movements are varied but often involve semi-purposeful thrashing of all four limbs, waxing and waning over many minutes, distractibility or interaction with the environment, prominent pelvic movements and back arching. Dissociative seizures may be difficult to differentiate from complex partial seizures of frontal lobe origin, which can present with very bizarre motor attacks. The key feature of the latter is that the episodes are usually stereotyped and occur during both wake and sleep.

Drop attack

Any cause of loss of awareness may proceed to a sudden collapse or drop attack. Epilepsy, syncope and other cardiovascular disorders are the more common causes of drop attacks.

Epilepsy

Sudden drop attacks are common in patients with learning disability and secondary generalized epilepsies. The falls may be tonic or atonic in nature and frequently cause severe facial injuries if the individual falls forwards.

Cardiovascular

If cerebral hypoperfusion is sufficient to cause sudden collapse there is usually loss of awareness (see above), but a drop attack may be the dominant presenting symptom.

Movement disorder

Most movement disorders that cause drop attacks have other more prominent features that make the diagnosis clear (e.g. Parkinson's disease). Paroxysmal kinesiogenic choreoathetosis may cause drop attacks if there is lower limb involvement.

Brainstem, spinal or lower limb abnormality

There are usually fixed neurological signs that give a clue towards the diagnosis. Tumours of the third ventricle, such as colloid cysts, may present with sudden episodes of collapse. Spinal cord vascular abnormalities may present with abrupt episodes of lower limb weakness leading to falls, without impairment of awareness.

Cataplexy

Cataplexy usually occurs in association with narcolepsy, although it may be the presenting clinical feature. There is no loss of consciousness with attacks. Attacks may be precipitated by emotion, especially laughter. Often there is only loss of tone in the neck muscles, with slumping of the head, rather than complete falls.

Metabolic disorder

Periodic paralysis caused by sudden changes in plasma potassium is rare. The condition may be familial or associated with other endocrine disorders or drugs. Usually there is a gradual onset, and the attacks last for hours.

Idiopathic drop attack

These attacks are most common in middle-aged females. They take the form of a sudden fall without loss of consciousness. Characteristically, the patients remember falling and hitting the ground. Recovery is instantaneous, but injury may occur.

Vertebrobasilar ischaemia

This condition is over-diagnosed and probably accounts for very few drop attacks. Typically, the attacks occur in the elderly, with evidence of vascular disease and cervical spondylosis. The attacks may be precipitated by head turning or neck extension resulting in distortion of the vertebral arteries and are of sudden onset, with features of brainstem ischaemia such as diplopia, vertigo and bilateral facial and limb sensory and motor deficits.

Transient focal motor attack

The most common cause of transient focal motor attacks is epilepsy. Tics may develop in adolescence. Paroxysmal movement disorders are rare, although unilateral paroxysmal kinesiogenic choreoathetosis may mimic motor seizures. Transient cerebral ischaemia usually presents with negative phenomena, although positive phenomena can occur with critical carotid stenosis. Tonic spasms of multiple sclerosis are usually seen in the context of other features of the illness, but may be a presenting feature.

Focal motor seizure

Focal motor seizures may involve jerking and posturing of one extremity, or reflect the spread of epileptic activity along the primary motor cortex. There is often associated paraesthesia. Following the attack, there may be localized transient weakness for seconds or minutes, sometimes longer. Seizures arising in many different brain regions may cause dystonic posturing.

Epilepsia partialis continua is a rare form of epilepsy that often causes diagnostic confusion. There is very frequent focal motor activity such as jerking of the hand or part of the face. This can persist for hours or days, continue into sleep, and may go on for years. The movements often become slow and pendulous, with some associated dystonic posturing.

Tics

Tics usually present with stereotyped movements in childhood or adolescence, sometimes restricted to one particular action (e.g. eye blinking) but may be multiple in nature. Tics may be confused with myoclonic jerks. They can be suppressed voluntarily, although to do so leads to a rise in psychological tension and anxiety which is then relieved by the patient allowing the tics to occur. Repetitive tics and stereotypies are particularly common in those with intellectual disability.

Transient cerebral ischaemia

Transient ischaemic attacks (TIAs) usually present with negative phenomena, i.e. loss of use of a limb, hemiplegia or other deficits, although positive phenomena such as paraesthesiae may occur. TIAs may last for a few minutes, but may persist for up to 24 hours. TIAs are not usually stereotyped or repeated with the frequency of epileptic seizures, and there are usually associated features to suggest vascular disease.

Tonic spasms of multiple sclerosis

These spasms usually occur in the setting of known multiple sclerosis, but may be the presenting feature, although other evidence of multiple sclerosis will usually be found on examination and investigation. The spasms may last for several seconds and sometimes longer than 1 minute.

Paroxysmal movement disorder

Paroxysmal kinesiogenic choreoathetosis may present with focal motor attacks that are very similar to epileptic seizures. Tremor can occur in a variety of movement disorders and is usually sufficiently persistent to make the non-epileptic nature clear, but may be difficult to distinguish from certain forms of epilepsia partialis continua. Myoclonus of subcortical origin may be suspected from the distribution of involved muscles (e.g. spinal myoclonus may be restricted to specific segments, either unilateral or bilateral). Peripheral nerve entrapment usually presents with weakness but occasionally can present with episodic jerks or twitches.

Transient focal sensory attack

Somato-sensory attack

Epileptic seizures involving the primary sensory cortex are less common than motor seizures, and may cause spreading paraesthesia. Seizures involving the second sensory areas or medial frontal cortex can cause sensory symptoms. There are usually other epileptic features because of involvement of adjacent or related brain structures. Transient sensory phenomena may also be seen in peripheral nerve compression or other abnormalities of the ascending sensory pathways, hyperventilation or panic attacks and in TIAs. TIAs are not usually stereotyped or repeated with the frequency of epileptic seizures, and there are usually associated features to suggest vascular disease.

Lesions of sensory pathways cause persistent symptoms, but diagnostic confusion may arise early on in the natural history, when complaints are intermittent, or if they are posture related. Hyperventilation may be associated with unilateral and localized areas of paraesthesia (e.g. one arm). Intermittent sensory illusions may be experienced in relation to amputated or anaesthetic limbs. Migrainous episodes may also cause localized areas of paraesthesia, but usually have the distinction of a gradual evolution of sensory phenomena, both positive and negative, and associated features of migraine.

Transient vestibular symptoms

Acute attacks of vertigo may occasionally be caused by a seizure in the parietal or temporal lobes. In these cases there are generally associated features that point to cerebral involvement, such as a focal somato-sensory symptoms, déjà vu or disordered perception. Peripheral vestibular disease is a much more common cause and may give rise to paroxysmal rotational vertigo and perception of linear motion and there are often also other symptoms of auditory and vestibular disease such as deafness, tinnitus, pressure in the ear and relation to head position.

Visual symptoms

Migraine is a common cause of episodic visual phenomena. The evolution is usually gradual, over several minutes, with fortification spectra and associated photophobia, nausea and headache. Epileptic phenomena are usually much shorter, evolving over seconds, and the visual hallucinations are more commonly of coloured blobs rather than jagged lines. On occasion, a migraine attack may be followed by an epileptic seizure.

Facial muscle and eye movements

Facial movements occur in many neurological conditions including partial seizures, tics, dystonias or other paroxysmal movement disorders, drug-induced dyskinesias and hemifacial spasm, and psychological disorders.

Partial seizures

Benign childhood epilepsy with centro-temporal spikes usually presents with seizures in childhood affecting the face, often with unilateral grimacing, hemibody sensory and motor phenomena, or secondarily generalized seizures occurring in sleep. Focal motor seizures may cause twitching of one side of the face which may be restricted to specific areas.

Complex partial seizures may cause automatisms with lip smacking, chewing, swallowing, sniffing or grimacing, with amnesia and impaired awareness. If these features are caused by seizure activity the attacks are usually relatively infrequent. Dystonia or other movement disorder episodes are likely to be more persistent or occur many times per day.

Movement disorders

Hemifacial spasm typically presents in the elderly or middle aged with clusters of attacks that initially involve the eye but subsequently spread to the rest of that side of the face. Facial weakness may develop and continue between attacks.

Bruxism may occur either during the day or in sleep, especially in children with learning disability. Episodes are usually more prolonged than with the automatisms of complex partial seizures, and there are no associated features to suggest an epileptic basis.

As with dystonia and other movement disorders affecting the face, there may be evidence of involvement elsewhere, and attacks are usually more frequent than is seen with isolated seizures.

Other neurological disorders

Defects of eye movement control are common in patients with a wide range of neurological disorders. There are usually associated features that indicate a non-epileptic basis. Bizarre eye movements also occur in blindness and may be mistaken for epileptic activity. Careful examination is required to ascertain the precise features of the eye movement disorder, and in particular any precipitating factors or features of cerebellar or brainstem disease.

Psychic experiences

Intermittent psychic phenomena can be seen in partial seizures (especially of temporal lobe origin), migraine, panic attacks, transient cerebral ischaemia, drug-induced flashbacks, or with illusions associated with loss of a sensory modality as well as psychotic illnesses.

Epilepsy

Partial seizures of temporal lobe origin are commonly associated with fear, déjà vu, memory flashbacks, visual, olfactory or auditory hallucinations. Other features include altered perception of the environment with a distancing from reality or change in size or shape of objects; altered language function; emotions such as sadness, elation and sexual arousal.

Psychic experiences may have some relation to past experiences. They are usually recalled as brief scenes, sometimes in a sequence. They are usually unclear, e.g. a patient may describe an illusion of someone standing in front of them who they know, but they cannot name them or describe them in detail. A rising epigastric sensation may occur alone or in association with such experiences. Elemental visual phenomena, such as flashing lights or coloured circles, are more often seen in occipital lobe epilepsy.

Migraine

Migrainous psychic phenomena may involve an initial heightening of awareness. The principal features are usually visual illusions which may be elemental or complex. They rarely have the same intense emotional components of temporal lobe illusions or hallucinations. The time course is usually more prolonged than with partial seizures, with an evolution over several minutes and there are associated features of a pounding headache, photophobia and nausea or vomiting. There may be identifiable precipitants, and there is often a relevant family history.

Panic attack

These are usually associated with feelings of fear and anxiety. Hyperventilation may lead to dizziness and light-headedness. There are often unpleasant abdominal sensations similar to the epigastric aura of partial seizures. The evolution, associated increases in heart rate and respiration, longer time course and history of precipitating factors usually make the diagnosis clear, but distinction from temporal lobe seizures may be difficult.

Drug-induced flashback

These share many of the qualities of psychic temporal lobe seizures. They are individualized hallucinations usually related to the circumstances of the drug abuse, often with emotional content of fear or anxiety. A careful history should be taken for substance abuse, especially LSD, psilocybin, peyote and mescaline.

Hallucination or illusion caused by loss of a primary sense

Hallucinations and illusions of an absent limb are well-recognized in amputees. Similarly, people who lose sight either in the whole or part field may experience visual hallucinations or illusions in the blind field. Such phenomena can be elemental or complex and include evolving scenes. Similar experiences can occur with deafness.

Such experiences resulting from the loss of a primary sense present particular diagnostic difficulty when they occur in the setting of a structural lesion, which could result in both phenomena. An occipital infarction, for example, could cause visual loss and could also give rise to epileptic seizures. Often the hallucinations caused by sensory loss are more prolonged, lasting for minutes or hours, but may be brief.

Psychotic hallucination and delusion

Hallucinations and delusions are the hallmark of psychotic illnesses. The following features would suggest a psychiatric rather than epileptic basis: complex nature with an evolving or argued theme, auditory nature involving instructions or third person language, paranoid content or associated thought disorder. Psychotic episodes are usually more longer lasting than isolated epileptic seizures, although intermittent psychosis may have a similar time course to non-convulsive status. Persistent mood changes may be a helpful guide, but even short temporal lobe seizures may be followed by mood changes lasting for hours or days. Furthermore, flurries of epileptic attacks may themselves cause an organic psychosis lasting for several days. Ruminations and pseudo-hallucinations, in which the patient retains some insight, can occur in affective disorders.

Dissociative seizure

Dissociative seizures may be associated with reports of hallucinations and illusions. Initially, the symptoms may seem plausible, but should be suspected if they are florid and multiple in type (e.g. auditory, olfactory and visual at different times) with evolving stories or patterns of expression.

Aggressive or vocal outburst

These are rarely epileptic in nature if they occur in isolation. They are especially common in adults and children with mental retardation. In this setting there is organic brain disease that could lower the overall seizure threshold. A not infrequent forensic issue is the occurrence of violent, or other, crimes in patients with epilepsy, in which it is a defence claim that the crime was committed in a state of automatism. Certain features are strong evidence against an epileptic basis to the attack:

- Absence of a prior history of epilepsy with automatisms;
- Premeditation and evidence of planning or preparation;
- Directed violence;
- Evidence of complicated and organized activity during the episode;
- Recall of events during the episode;
- Witness accounts not indicative of a disturbance of consciousness; and
- Subsequent attempts at escape or concealment of evidence.

Episodic phenomena in sleep

Attacks occurring during sleep present particular diagnostic difficulties because they are often poorly witnessed, and the patient may have little, if any, recall of the event or the preceding circumstances.

Normal physiological movement

Whole body jerks commonly occur in normal subjects on falling asleep. Fragmentary physiological myoclonus usually involves the peripheries or the face, and occurs during stages 1 and 2 and REM sleep. Periodic movements of sleep may be an age-related phenomenon, being seen in less than 1% of young adults, but occurring with increasing frequency during middle and old age such that they are present in perhaps half of the elderly population. Typically, these movements occur at regular intervals of 10–60 seconds and may occur in clusters over many minutes.

Frontal lobe epilepsy

Frontal lobe seizures can display specific sleep-related characteristics causing diagnostic confusion. Such attacks are often frequent, brief, bizarre and may only occur during sleep. Attacks may include apnoea, dystonic, myoclonic or choreiform movements which may be unilateral or bilateral, and some retention of awareness. The attacks are scattered throughout the night, and usually arise from non-REM sleep. Frequency is highly variable, but some patients have more than 20 attacks in a night. An important clue to the diagnosis is the occurrence of additional secondarily generalized seizures and seizures occurring in wakefulness.

Other epilepsies

Seizures arising in other brain regions may present with nocturnal attacks. Patients may be aroused by an aura, although often this is not recalled when attacks arise from sleep. Complex automatisms, in which patients get out of bed and wander around, may cause confusion with parasomnias. With nocturnal seizures of any type the partner is frequently awoken by particular components, such as vocalization, and does not witness the onset. Generalized tonic–clonic seizures not uncommonly occur on or shortly after awakening.

Pathological fragmentary myoclonus

Excessive fragmentary myoclonus persisting into sleep stages 3 and 4 may be seen with any cause of disrupted nocturnal sleep.

Restless leg syndrome

The restless leg syndrome is characterized by an urge to move the legs, especially in the evening when lying or sitting. It may be associated with various unpleasant paraesthesiae. All patients with restless legs have periodic movements of sleep. These may be severe and can also occur during wakefulness. In addition, there may be a variety of brief daytime dyskinesias.

Non-REM parasomnia

This involves night terrors or sleep walking. Non-REM parasomnias usually present in childhood or adolescence, and are often familial. The attacks arise from slow wave sleep, typically at least 30 minutes, but not more than 4 hours, after going to sleep and the timing is often consistent. Attacks may be spaced out by months or years and rarely occur more than once per week, and usually no more than one attack occurs in a single night. They are more likely after stressful events, or when sleeping in a strange bed.

Night terrors involve intense autonomic features (sweating, flushing, palpitations) and a look of fear. Patients may recall a frightening scene or experience, but do not usually recount a vivid dream prior to the attacks. Certainly children do not recall events. They may be difficult to arouse, and confused for several minutes. Vocalizations are common. Sleep walking may involve getting out of bed and performing complex tasks. Sometimes it is possible to lead the patient back to bed without awakening. They may respond if spoken to, but their speech is usually slow or monosyllabic. Brief abortive episodes are more common, involving sitting up in bed with fidgeting and shuffling (mimicking a complex partial seizure). Non-REM parasomnias may cause self-injury but rarely directed aggression. They are associated with enuresis.

REM parasomnia

REM parasomnia usually occurs in middle age or the elderly, and shows a marked male predominance. It more often occurs in the later portion of sleep. During REM sleep, patients may have an increase in the frequency or severity of fragmentary myoclonus, thrash about, call out, display directed violence or appear to enact vivid dreams. Attacks may last from seconds to minutes. If awoken, patients may recall part of these dreams. Although REM sleep behaviour disorders may occur in healthy elderly subjects, they are also seen in association with drugs (e.g. tricyclics) or alcohol, or CNS diseases such as multi-system atrophy. The possibility of REM sleep disorders needs to be considered both at initial presentation, and also in patients known to have CNS disorders.

Sleep apnoea

Patients with sleep apnoea usually present with daytime hypersomnolence. However, the apnoeic episodes can cause episodic grunting, flailing about or other restless activity that can appear to mimic nocturnal epilepsy. Occasionally, the resultant hypoxia precipitates secondary seizures.

Other movements in sleep

Nocturnal body rocking may occur in patients with learning disability, or following head injury. In patients with many different forms of daytime dyskinesias, similar movements may occasionally occur during overnight sleep, usually in the setting of brief arousals.

Prolonged confusional or fugue state

Epileptic seizures usually last for seconds or minutes. After generalized tonic–clonic seizures (or, less often, complex partial seizures) there may be confusion lasting for many minutes, but rarely more than an hour. Such episodes only present diagnostic difficulty if the initial seizure is unwitnessed. Nevertheless, epileptic states can last for longer periods of time, as can other types of cerebral disorder and the differential diagnosis of prolonged epileptic confusional states (non-convulsive status) should include acute encephalopathy, non-convulsive status epilepticus, transient global amnesia, intermittent psychosis and dissociative seizures.

Acute encephalopathy

Virtually any severe metabolic disturbance can cause an acute encephalopathy (e.g. diabetic ketoacidosis; hypoglycaemia; respiratory, renal or hepatic failure; drug ingestion; hyperpyrexia; sepsis). Transient metabolic disturbances are most often seen in treated diabetes mellitus resulting from insulin-induced hypoglycaemia. Occasionally, metabolic disorders, such as porphyria and urea cycle enzyme defects, may present with exacerbations with symptoms lasting for hours or days and may give the appearance of an episodic condition. Acute neurological conditions also need to be considered, particularly encephalitis, meningitis, other intracranial infection, head injury, cerebral infarction or haemorrhage. Drug abuse can cause isolated episodes or recurrent bouts, related to intoxications.

Non-convulsive status epilepticus

Patients with complex partial seizures, typical or atypical absences may present with prolonged confusional states caused by complex partial epilepticus or absence status. Such attacks may be the first manifestation of the seizure disorder, or occur in the setting of known epilepsy.

Intermittent psychosis

Although usually more sustained, psychiatric disorders may present with episodes of delusions, hallucinations or apparent confusion, lasting for hours or days.

Transient global amnesia

These episodes typically commence acutely, and last for minutes or hours and involve both retrograde and anterograde amnesia. Patients may perform complex activities, but afterwards have no recall of them. There is a lack of other neurological features to the attacks, and consciousness appears to be preserved. During an attack, the patients do not appear overtly confused. The attacks may involve bilateral medial temporal dysfunction, which in some patients may be on the basis of ischaemia, while others may have an epileptic basis.

Hysterical fugue

A fugue state may arise without an organic physical cause, as a conversion symptom. These episodes may be brief or very prolonged, lasting for days or even weeks. If seen during the episode, inconsistencies are often found on examination of the mental state. There is usually a history of serious psychiatric disturbance or alcohol or dug abuse. In some cases, the question of malingering arises, most commonly in a situation in which the person's state prevents questioning by law officers and when the subject professes no memory of events. The diagnosis is more difficult to identify if the patient is only seen subsequently. The matching of witness accounts and the apparent sequence of events is essential, but it may remain difficult to come to a firm conclusion.

Investigation of epilepsy

Electroencephalography

Electroencephalography (EEG) was introduced into clinical practice in the early 1940s, and has since developed into an array of digitally based techniques, integrated with video and other investigative modalities. However, like all investigations, it has limitations which must be recognized, and its applications should be targeted to specific clinical questions (Table 6.12).

Clinical questions that can be addressed by EEG

EEG in the diagnosis of epilepsy

EEG is the primary investigation in epilepsy. However, it should not be forgotten that the diagnosis of epilepsy is essentially clinical, and EEG has a high false negative rate and a low but important false positive rate. EEGs are liable to misinterpretation when there is insufficient knowledge of the range of normal and nonspecific EEG phenomena – this has repeatedly been identified as a common reason for false diagnosis of epilepsy.

Up to about half of patients with epileptic disorders may have one normal interictal EEG, and around 10% of patients with epilepsy never show interictal spikes. A normal or negative EEG cannot therefore be used to rule out the clinical diagnosis of an epileptic seizure. Specificity of EEG in epilepsy is higher than its sensitivity, but a small percentage of otherwise normal subjects may show epileptiform abnormalities in their EEG. The incidence of epileptiform discharge is around 0.5% in adults with no known history of epilepsy, and about 2–4% in children. Epileptiform phenomena may also be seen in 10–30% of patients who have neurological disorders or cerebral pathologies (e.g. tumour, head injury, cranial surgery), without a history of seizures. Thus, an abnormal EEG showing epileptiform activity does not in itself indicate that the subject must have a seizure disorder.

Table 6.12 Use of electroencephalography (EEG) in clinical practice.

Diagnosis of epilepsy	Management of seizure disorders
Is the paroxysmal event an epileptic seizure?	Probability of recurrence after single unprovoked seizure
Is seizure onset focal or generalized?	Why has cognitive function deteriorated?
Syndromic classification	Is behavioural change brought about by non-convulsive status?
Identification of seizure triggers,	Likelihood of seizure recurrence after AED withdrawal

AED, antiepileptic drug.

Epileptiform phenomena

EEG features classified as epileptiform are spike discharges, spike or polyspike wave complexes, and sharp waves. The appearance of epileptiform discharge depends on the degree of neuronal synchronization and how the discharge spreads through cortex. Some epileptiform phenomena – 3 per second spike-wave discharge, hypsarrhythmia and generalized photoparoxysmal responses – are strongly correlated with clinical epilepsy. Others, such as focal sharp waves in centro-temporal regions, are moderately correlated with clinically evident seizures. The EEG of normal subjects can show a range of spikey features that resemble epileptiform activity, particularly in sleep. Physiological or pathological but non-epileptogenic variants include wicket spikes, 14 and 6 Hz spikes, rhythmic mid-temporal theta, and subclinical rhythmic epileptiform discharge in adults (SREDA). These variants mostly have no link with epilepsy, but are a potential source of confusion and EEG misinterpretation.

Location of electrodes and site of epileptic focus, age of patient, the presence of medication, diurnal timing of the EEG and the frequency, severity and type of epilepsy all influence the chance of detecting epileptiform discharges. The timing of EEG in relation to last seizure event may be relevant and one study has found that an interictal EEG within 24 hours of a seizure revealed an abnormality in 51% compared to 34% who had later EEG.

Routine EEG testing

A routine interictal EEG recording typically takes 20–30 minutes, and should include standard activation procedures of hyperventilation and photic stimulation, following published protocols. Most EEG departments use the international 10–20 system of scalp electrode placement, but additional electrodes are often useful, especially to record from the anterior temporal lobe region (superficial sphenoidal electrodes). The combination of wake and sleep records gives a yield of 80% in patients with clinically confirmed epilepsy. Sleep EEG can be achieved by recording natural sleep, or with hypnotics to induce sleep. Whether sleep deprivation has additional value for induction of epileptiform activity is unclear, but there is some evidence that it specifically activates spikes in IGEs. Evaluation of different EEG protocols in young people (<35 years) with possible epilepsy found that sleep-deprived EEG provided significantly better yield than routine

EEG or drug-induced sleep EEG, and it may be the most cost-effective protocol for investigation of new epilepsy.

Prolonged interictal sampling using long-term monitoring increases diagnostic yield by about 20%, and many EEG departments now offer 24-hour ambulatory multi-channel digital EEG. Other methods include repeating EEG at different times of day and 60–120 minute out-patient EEG. After a first seizure, the pick-up rate depends on the syndrome and seizure type.

The National Institute for Clinical Excellence (NICE) guidelines for diagnosis and management of the epilepsies in adults and children recommend that routine EEG should be performed in adults in whom the clinical history suggests an epileptic seizure. In children, EEG is recommended after a second seizure, as the diagnostic yield from routine EEG after a single seizure is considered too low to influence management.

EEG in the classification of epileptic seizures and syndromes

Clinical criteria alone may not be sufficient for characterization of epilepsy type, or infallible. Both epileptiform activity and interictal background cortical rhythms provide information that can complement the history and aid diagnosis. EEG findings contribute to diagnostic refinement at different levels: by establishing whether the seizure disorder is focal or generalized, idiopathic or symptomatic, or part of an epilepsy syndrome.

Although division of seizure types into partial and generalized is a cornerstone of clinical practice, it is important to appreciate there can be EEG (and clinical) overlap between the two. Rapid generalization of epileptiform activity secondary to a symptomatic focus can mimic idiopathic generalized epilepsy; focal spikes and regional accentuation of generalized spike-wave discharge are well-recognized in IGE syndromes.

Idiopathic generalized epilepsy

The typical EEG findings in IGE are generalized spike or polyspike and slow wave discharges at 3–5 Hz (Figure 6.1), normal background cortical rhythms and a relatively high occurrence of photosensitivity. In childhood absence epilepsy, with typical absence seizures, there is characteristic bilateral synchronous 3-Hz spike wave, usually lasting 5–10 seconds. Background cortical rhythms are normal, but some children show runs of occipital rhythmic delta (up to 40% of cases), which may persist after remission of absences. Photosensitivity is uncommon (less than 10%), and possibly indicative of poorer prognosis. Patients with juvenile absence epilepsy usually show polyspike discharge or spike-wave frequency above 3 Hz. In juvenile myoclonic epilepsy, the interictal and ictal EEG characteristic is brief bursts of polyspike (sometimes single spike) and wave discharge. Variable asymmetry of the discharge is common, and interictal focal abnormalities occur in up to 40%, and photosensitivity in 40–50%. Not all patients with IGE show typical electrographic findings in the first EEG. Generalized absence epilepsy is most likely to show diagnostic EEG abnormalities at initial investigation, whereas other syndromes may need serial recording to elucidate diagnosis. This should not delay appropriate treatment.

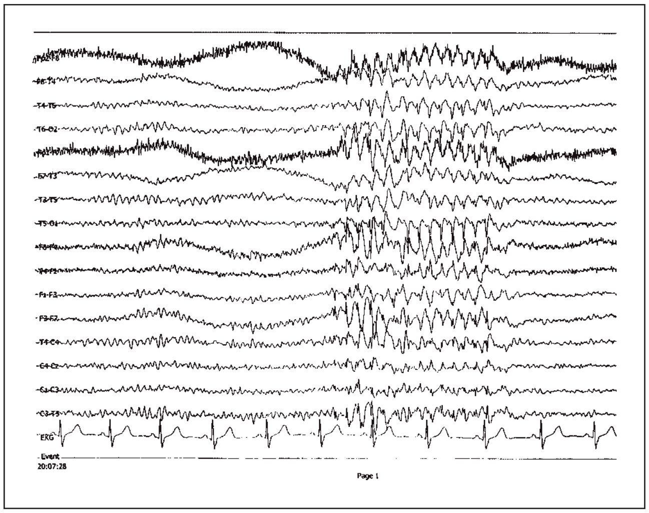

Figure 6.1 Typical spike wave discharge in a patient with absence epilepsy.

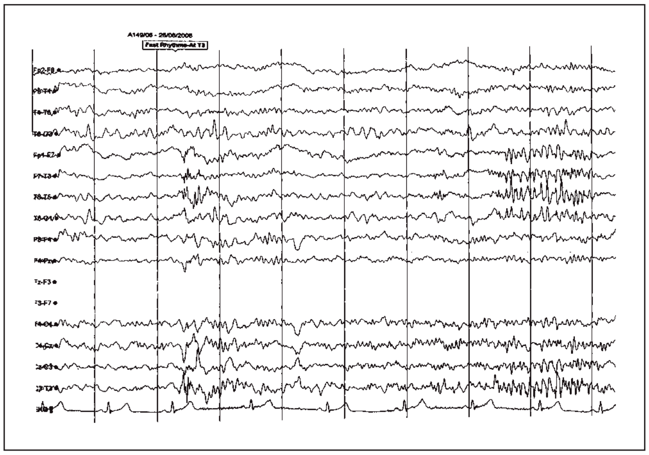

Figure 6.2 High-frequency interictal discharge in a patient with neocortical or lateral temporal lobe epilepsy.

IGE can present in adult life. Most cases have either generalized tonic–clonic seizures with or without myoclonus, and electro-clinical manifestations are similar to those in IGE presenting in the more classic age groups.

Typical absence seizures in IGE should be distinguished from atypical absences that occur in the epileptic encephalopathies. The EEG signature of this seizure type is a relatively slow (<2.5 Hz) and less regular spike-wave discharge, and the EEG shows abnormalities of background cerebral activity, in keeping with the mainly severe symptomatic generalized epilepsies, in which these types of absences occur.

Benign childhood epilepsy syndromes

The EEG is diagnostic of benign childhood epilepsy with centro-temporal spikes, the characteristic being high-amplitude focal sharp wave discharges in central and temporal regions, either bilateral or unilateral, and potentiated by sleep. A few children show focal discharges in other brain regions or generalized spike-wave activity. Background cerebral rhythms are normal. The EEG is often very abnormal even in the presence of infrequent (or indeed any) seizures. Benign childhood occipital epilepsy (BCOE) has more variable EEG features; paroxysms of occipital spike-wave on eye closure (fixation off sensitivity) are typical of the early onset form or Panayiotopoulos syndrome. Otherwise, multifocal discharges, rolandic spikes and generalized spike wave are common. The clinician should be alerted to a diagnosis of BCOE in a child with infrequent seizures or paroxysmal autonomic symptoms whose routine EEG shows frequent multi-focal discharges.

Electrical status epilepticus in sleep

This condition is defined by the presence of continuous spike-wave discharge occupying 85% or more of the sleep record. It occurs in a number of childhood epilepsies, including the Landau–Kleffner syndrome of acquired aphasia and epilepsy.

Progressive myoclonic epilepsies

These epilepsies show generalized spike-wave discharge, photosensitivity, 'giant' sensory-evoked potentials (SEPs), facilitation of motor-evoked potentials (MEPs) by afferent stimulation, and abnormalities of background cerebral activity, typically an excess of slow activity. The background abnormalities are usually progressive, particularly in syndromes with dementia or significant cognitive decline such as Lafora body disease. Some specific features occur in some cases: vertex sharp waves in sialidosis, occipital spikes in Lafora body, and giant visual-evoked potentials (VEPs) in lipofuscinosis.

Partial epilepsy

Broadly speaking, localized EEG changes are more common in temporal lobe partial epilepsy than in extratemporal epilepsies (Figures 6.2 and 6.3), and spiked and/or high-frequency discharge is more likely to occur in foci that are located superficially in neocortex. Interictal EEG can be normal or non-localizing in partial epilepsies if the epileptogenic region is:

1. Extensive;
2. Remote from scalp electrodes, e.g. mesial frontal lobar areas;
3. Involves too small a neuronal aggregate for synchronized activity to be registered on the scalp.

In partial epilepsies, the most important ictal EEG changes for seizure localization are those that occur within the first 30 seconds after the seizure onset. Later changes are of limited value for localization or lateralization of the epileptogenic region, because the discharge will by then have propagated to other brain areas.

Temporal lobe epilepsy

Mesial temporal lobe epilepsy (TLE) associated with unilateral temporal lobe pathology, usually hippocampal sclerosis, shows anterior and mid temporal interictal spikes, and a characteristic rhythmic 5–7 Hz ictal discharge accompanying seizures in 80%. Post-ictal ipsilateral slow activity and potentiation of spikes can also help to lateralize the epileptogenic region. Independent bitemporal interictal spikes are common, but predominate over the pathological temporal lobe in 60% of cases. Frequent or dominant spikes over the contralateral temporal lobe are associated with poorer seizure outcome after temporal lobectomy.

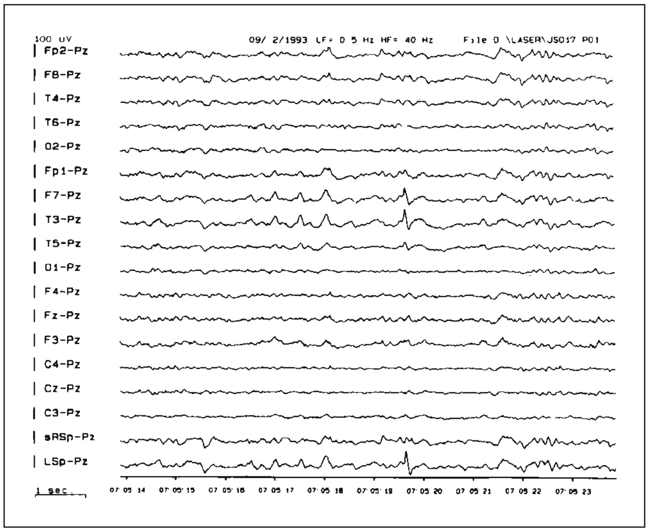

Figure 6.3 Interictal EEG: left mesial temporal lobe epilepsy, referential recording. Focal spikes at electrodes sited near the left anterior temporal lobe (F7 and Sp1) and mid temporal lobe (T3).

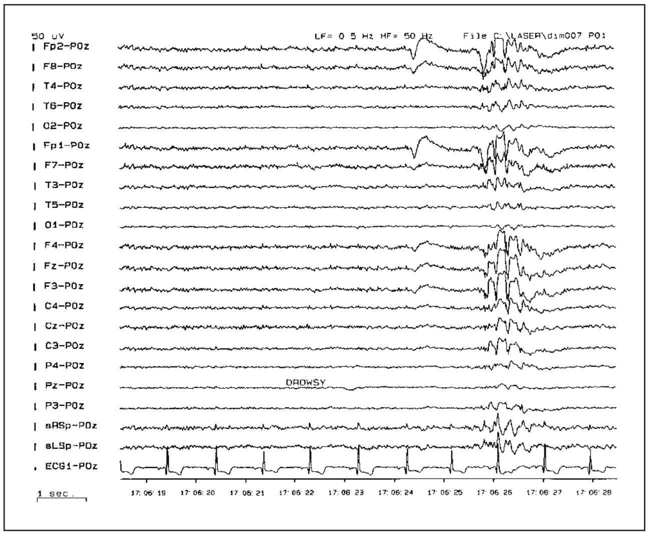

Figure 6.4 Widespread bilateral spike-wave discharge in a man with frontal lobe complex partial seizures (hypermotor semiology).

In lateral temporal lobe epilepsies, interictal spikes tend to be located over the mid and posterior temporal lobar regions; the ictal EEG discharge is typically high frequency, and lateralized in about 50% of cases.

Frontal lobe and other extratemporal epilepsies

Focal interictal EEG abnormalities are the exception, and there are no specific patterns associated with the subtypes of frontal lobe epilepsy. Many patients show widespread or even generalized abnormalities (Figure 6.4), because of rapid spread to other lobar regions and secondary generalization. The same is true for ictal changes, the most common pattern in frontal lobe epilepsy being either high-amplitude slow or a diffuse fast discharge followed by generalized attenuation and/or bilateral slow activity.

EEG localization in extratemporal symptomatic partial epilepsy of parietal and occipital lobe is limited for the same reasons as frontal lobe epilepsy, and the majority of patients with simple partial seizures manifesting with sensory symptoms will have negative scalp EEGs.

EEG and prediction of seizure recurrence

If the initial EEG shows definite epileptiform discharge, there is a greater risk of seizure recurrence in individuals presenting with the first unprovoked seizure, particularly if idiopathic in type. EEG has distinguished between high and low risk groups in a number of studies: one systematic review showed risk of recurrence at 2 years was 27% if the EEG was normal, but 58% if the epileptiform activity was present.

EEG and withdrawal of antiepileptic medication

The type of epilepsy syndrome is the most important variable in predicting likelihood of seizure recurrence for patients in remission who are considering withdrawal of medication. EEG can provide supplementary information: presence of spike-wave discharge in patients with IGE and evidence of a generalized photosensitive response/photoparoxysmal response are associated with high risk of recurrence. The prognostic significance of other patterns and abnormalities in other types of epilepsy is less clear.

EEG and antiepileptic drugs

Acute administration of barbiturates and benzodiazepines suppresses interictal discharge, but the effect declines when these drugs are given as chronic therapy. Sodium valproate suppresses generalized spike-wave and photoparoxysmal responses, and EEG can be used to monitor therapeutic efficacy. Lamotrigine may have a similar effect, and ethosuximide also suppresses generalized discharges. Other antiepileptic drugs have variable or inconsistent effects on either focal or generalized epileptiform activity, and EEG is therefore of little or no use in monitoring response to drug treatment. 'Treating the EEG' is generally undesirable.

Antiepileptic drugs can affect background cortical rhythms, but significant slowing does not occur unless there is drug toxicity.

Long-term EEG monitoring

Long-term monitoring (LTM) allows extended EEG recording, which can be undertaken as an ambulatory procedure using a portable recorder, or via hard wired recorders with time-linked video in a hospital setting. Usually, the aim is to document 'attacks' rather than the interictal state. LTM has been shown in several studies to change diagnosis and affect management in >50% of difficult to treat cases. Its principal applications are shown in Table 6.13.

Ambulatory EEG monitoring is most suited to clinical problems that do not require concurrent synchronized video to document clinical features, or for monitoring in a specific environment. In-patient video EEG telemetry units have specialized staff who are experienced in the identification of subtle clinical events and care of patients during seizures. These units are the safest environment for reduction in medication dose to provoke seizures. The optimal length of study for LTM depends on the clinical problem, and frequency of attacks – if it is less than once per week, LTM is not likely to be beneficial.

Neurophysiology for assessing patients for epilepsy surgery

Interictal and ictal EEG are pivotal investigations in presurgical evaluation, but are generally more important in resective surgical procedures than in functional procedures such as callosotomy and vagal nerve stimulation (Table 6.14).

The number of seizures that need to be recorded varies from case to case, and depends to some extent on the localizing strength of other data. Most epilepsy surgery candidates can be adequately investigated by scalp interictal and ictal EEG, but complex cases

Table 6.13 The principal clinical applications of long-term electroencephalogram (EEG) monitoring.

Differential diagnosis of paroxysmal neurological attacks
Distinction between nocturnal epilepsy and parasomnias
Diagnosis of psychogenic non-epileptic seizures
Characterization of seizure type and the electro-clinical correlates of epileptic seizures
Quantification of epileptiform discharge and seizure frequency
Evaluation in epilepsy surgery candidates
Identification of sleep-related epileptiform discharge/electrical status in children
Electro-clinical characterization of neonatal seizures
Monitoring of status epilepticus (convulsive, non-convulsive, electrographic)

Table 6.14 Aims of neurophysiological assessement in pre-operative evaluation.

Ensuring seizures are epileptic (a small percentage of patients in surgical programmes have co-morbid psychogenic non-epileptic seizures)
Documentation of electro-clinical seizure features, to show concordance with other data
Demonstration of epileptogenicity in the presumed pathological substrate
Identification of possible other epileptogenic foci
Functional assessment using cortical stimulation when pathology is located in or close to eloquent cortex

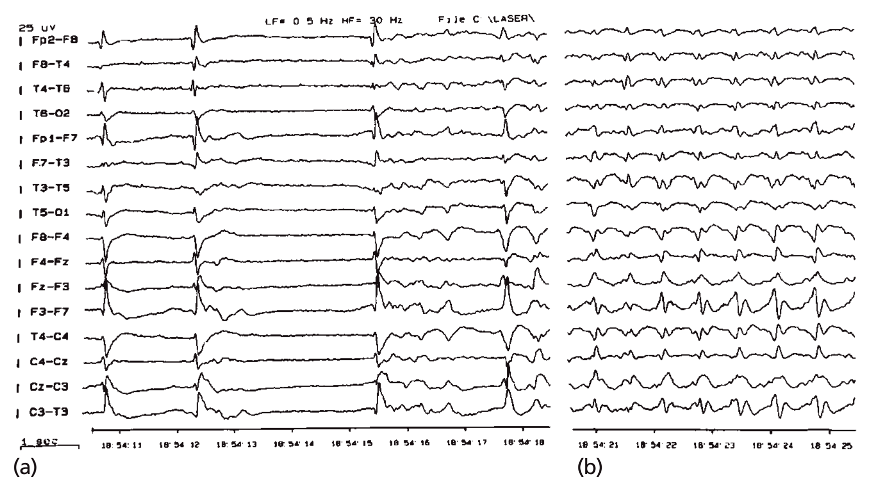

Figure 6.5 Segments from EEG monitoring in convulsive status: (a) burst suppression and some breakthrough discharge; (b) electrographic status.

may need invasive neurophysiological studies. The usual indications for invasive EEG are dual or possible multiple potential epileptogenic pathologies, bilateral hippocampal sclerosis, focal lesions in eloquent cortex, and individuals with negative neuroimaging in whom other investigations have suggested likely location of the epileptogenic region. Invasive EEG uses a range of electrode types (depth, strip, grid) inserted neurosurgically. Electrode choice and placement is determined by where the epileptogenic region is sited: subdural grids are best for coverage of a large area of cortex, depth electrodes are more suited to deeper lying foci. Cortical stimulation can be performed with any of these intracranial electrodes. The main risks of invasive EEG are haemorrhage and infection.

EEG and status epilepticus

EEG is essential for diagnosis and management of status epilepticus in convulsive (Figure 6.5) and non-convulsive forms. As a minimum standard, EEG should be performed within 12–24 hours for admissions with uncontrolled seizures or confusional states, and before transfer to intensive care unit (ICU). EEG monitoring should be available during treatment of refractory status. There are generally no specific EEG markers of the different electro-clinical types of status: all show variations of waxing and waning rhythmic patterns, with or without frank epileptiform discharges.

EEG is used in convulsive status epilepticus to:

1 Confirm status and exclude pseudostatus;

2 Differentiate causes of altered mental status – continuing seizures, drug-induced coma or encephalopathy; and

3 In the refractory stage to monitor and guide treatment, as clinical manifestations of ongoing seizure activity may then be subtle or absent.

The usual end-point of anaesthetic treatment is burst suppression (Figure 6.5), but seizure suppression may be sufficient in patients unable to tolerate higher dose anaesthesia. EEG may also contribute information of prognostic value: continuing electrographic status after the convulsive phase is associated with worse outcome in convulsive status.

Non-convulsive status epilepticus

This incorporates a range of conditions, with variable clinical features and causes. EEG is necessary for diagnosis of non-convulsive status epilepticus (NCSE), especially when the clinical manifestations are subtle. The EEG expression of non-convulsive status depends on cause, and includes any of continuous spike-wave discharge (generalized in absence status epilepticus), discrete localized electrographic seizures, diffuse slow activity with or without spikes, and periodic and/or repetitive epileptiform discharge (ED). Electrographic confirmation of NCSE is often difficult in simple partial status, when the EEG is unchanged or non-specific; in epileptic syndromes, such as Lennox–Gastaut syndrome, where there is overlap of ictal and interictal EEG patterns; and in patients with acute cerebral damage, e.g. caused by infection or trauma, because EEG abnormalities may be directly related to the primary pathology. Preferably, EEG should be recorded during acute administration of intravenous benzodiazepine or other antiepileptic therapy to confirm effective treatment of NCSE.

When should EEG be performed in the intensive care patient?

EEG has three main roles in the ICU patient. First, it can be used to distinguish coma from diminished responsiveness resulting from other causes (psychiatric, sedation, neuromuscular, locked in syndrome); secondly, to detect non-convulsive or clinically subtle seizures (most cases of status on the ITU are non-convulsive or difficult to identify on clinical grounds alone); thirdly, to identify an encephalopathy.

Cognitive deterioration

Acute confusional states or acute and/or subacute cognitive decline in epilepsy may be due to frequent subtle or clinically unrecognized seizures; a marked increase in epileptiform discharge; a metabolic or toxic encephalopathy; or non-convulsive status. EEG can be very helpful in determining the cause in acute confusional states, but is less likely to be useful in chronic cognitive decline other than to confirm an organic brain syndrome.

Imaging in epilepsy

X-ray computed tomography

MRI is generally the imaging modality of first choice for epilepsy. X-ray computed tomography (CT) is useful in acute situations when MRI is not appropriate. CT is also helpful to identify focal cortical calcification and in diagnosing tuberous sclerosis and Sturge–Weber syndrome. CT is not as sensitive and specific as MRI for identifying common epileptogenic abnormalities, such as indolent gliomas, cavernomas, malformations of cortical development (MCD) and lesions in the medial temporal lobe. CT is also helpful where there are contraindications to MRI, such as a cardiac pacemaker or cochlear implants.

Magnetic resonance imaging

Most patients who develop epilepsy or whose chronic epilepsy has not been fully assessed should be investigated with MRI. The ILAE commission suggested the following indications for MRI in the investigation of patients with epilepsy, although these will depend on availability and clinical circumstances:

- Focal onset of seizures;
- Onset of generalized or unclassified seizures in the first year of life, or in adulthood;
- Focal deficit on neurological or neuropsychological examination;
- Difficulty in obtaining seizure control with first-line antiepileptic drugs; or
- Loss of seizure control or change in the seizure pattern.

In patients with newly diagnosed epilepsy, MRI identifies a causal epileptogenic lesion in 12–14%. MRI is not required in patients with a definite electroclinical diagnosis of idiopathic generalized epilepsy, or benign childhood epilepsy with centrotemporal spikes, who go into early remission. In chronic epilepsy, MRI detects lesions in up to 50–70%.

All patients with intractable epilepsy considered for surgery should undergo high-resolution structural MRI as the success of surgery is directly related to the ability to pinpoint the site of seizure onset and underlying structural abnormalities. A structural abnormality does not necessarily indicate the site of seizure origin, and clinical EEG and other data need to be correlated with imaging. Postoperative MRI is useful to identify the extent of a cortical resection or the presence of residual pathology, particularly if seizures continue after surgery.

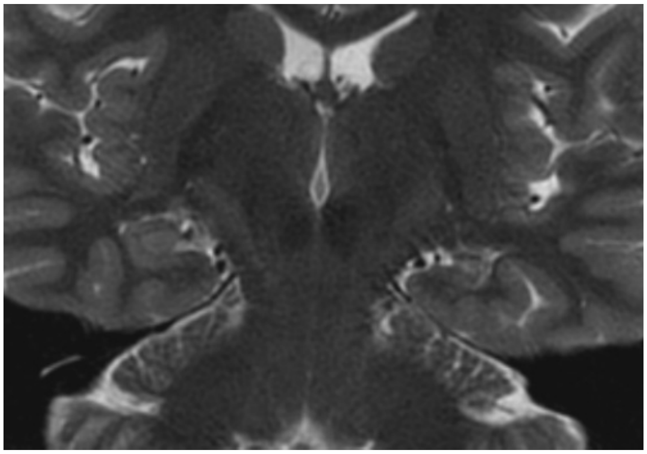

Figure 6.6 Left hippocampal sclerosis. Coronal T2-weighted image showing atrophy and increased T2 signal in the left hippocampus. The right hippocampus is normal.

Hippocampal sclerosis

The hippocampus is best visualized by acquiring thin slices (1–3 mm) orthogonal to its long axis. The primary MRI features of hippocampal sclerosis are hippocampal atrophy, demonstrated with coronal T1-weighted images, and increased signal intensity within the hippocampus on T2-weighted images (Figure 6.6). Additionally, decreased T1-weighted signal intensity and disruption of the internal structure of the hippocampus may be present. Other MRI abnormalities associated with hippocampal damage include atrophy of temporal lobe white matter and cortex, dilatation of the temporal horn and a blurring of the grey–white border in the temporal neocortex. Atrophy of the amygdala and entorhinal cortex variably accompany hippocampal damage but may also occur in patients with TLE and normal hippocampi. FLAIR images provide an increased contrast between grey and white matter, and facilitate differentiation of the amygdala from the hippocampus.

Visual assessment can reliably detect hippocampal volume asymmetry of more than 20%; however, lesser degrees of asymmetry require quantitative volumetric analysis. The use of contiguous thin slices increases the reliability of measurements and permits localization of atrophy along the length of the hippocampus. Hippocampal volumes need to be corrected for intracranial volume to identify symmetrical bilateral atrophy. Patients with unilateral hippocampal volume loss, no other imaging abnormality and concordant clinical and EEG data have more than 70% chance of being seizure free after surgery. Measurement of T2 relaxation time is another objective way to assess hippocampal damage. The advantage of this technique is that hippocampal T2 (HT2) times are absolute values, which can be compared against control data. Increased HT2 reflects gliosis and neuronal loss. HT2 prolongation also correlates with the hippocampal volume loss. Both volumetry and T2 relaxometry techniques can be used to identify subtle amygdala pathology.

Malformations of cortical development

There are many forms of malformations. The MRI features of focal cortical dysplasia (FCD) are focal cortical thickening, simplified gyration, blurring of the cortical–white matter junction, and T2 prolongation in the underlying white matter, which forms a cone tapering towards the lateral ventricle. This is particularly well seen with a thin slice FLAIR acquisition. Complete surgical removal of FCD is accompanied by a 30–50% remission rate, but the epileptogenic zone may be more extensive than the abnormality visible on MRI. The abnormalities may be subtle and only be evident if optimal MRI techniques are used. Polymicrogyria with an excessive number of small and prominent convolutions is a frequently identified MCD that develops secondary to abnormal late migration. Several syndromes of region-specific symmetric polymicrogyria have been reported, and some have been linked to specific genetic loci. Schizencephalia (cleft brain) is often found in MRI in conjuction with polymicrogyria. Periventricular heterotopia has a characteristic MRI appearance (Figure 6.7).

Primary brain tumour

Patients with low-grade primary brain tumours frequently have intractable focal seizures as a presenting symptom. Underlying histopathologies include dysembryoplastic neuro-epithelial tumours, ganglioglioma, gangliocytoma, and pilocytic and fibrillary astrocytoma. Most lesions have low signal on T1- and high signal on T2-weighted images, and are not usually associated with vasogenic oedema. Complete resection of the neoplasm and overlying cortex results in successful control of seizures in most cases.

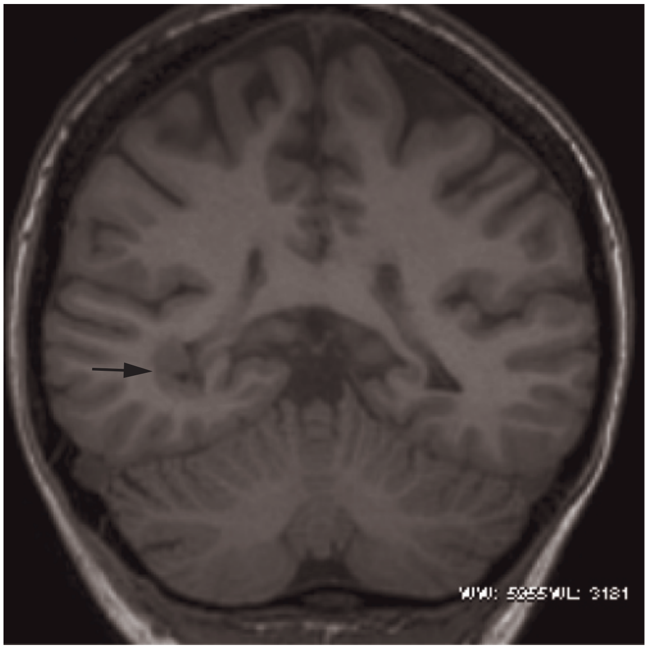

Figure 6.7 Subependymal heterotopia on the right (arrow) in coronal IR_{prep} T1-weighted image. Nodules of grey matter density are shown in the wall of the lateral ventricle.

Dysembryoplastic neuro-epithelial tumours are benign developmental tumours with features of a focal circumscribed cortical mass which may indent the overlying skull. Cyst formation and contrast enhancement may occur. Some cases calcify and may be more readily demonstrated with X-ray CT. Confident differentiation from low-grade astrocytomas and gangliogliomas is not possible by MRI.

Vascular malformation

Cavernous haemangiomas (cavernomas) are relatively common lesions which are important to identify as they are often surgically resectable. Most cavernous haemangiomas are not visible on CT but are identified on MRI scanning. The lesions are circumscribed and have the characteristic appearance of a range of blood products on MRI (Figure 6.8). The central part contains areas of high signal on T1- and T2-weighted images, reflecting oxidized haemoglobin, with darker areas on T1-weighted images as a result of deoxyhaemoglobin. The ring of surrounding haemosiderin appears dark on a T2-weighted image. Up to 50% of cavernous malformations are multiple, and may occur on a familial basis. AVMs with high blood flow have a different and distinctive appearance with a nidus, feeding arteries and draining veins.

Acquired damage

Focal or diffuse cortical damage can develop as a consequence of trauma, infarction or infection of the CNS. Cerebrovascular disease associated with epilepsy is particularly common in older age groups. Worldwide, neurocysticercosis and tuberculomas are the most common causes of intractable focal epilepsy. These lesions have typical appearances on MRI which evolve with time and which, unless calcified, may resolve.

Functional magnetic resonance imaging

Functional MRI (fMRI) can visualize regional brain activity. The areas detected with changes in blood oxygenation level-dependent (BOLD) contrast that occur during cognitive, sensory and other tasks, and allow the mapping of networks involved in the performance of these tasks. The most important clinical application of fMRI is in the localization and lateralization of cognitive functions of epilepsy patients evaluated for surgery in order to minimize the risk of causing a fixed deficit. However, the studies require patient cooperation, both in performing tasks and limiting motion. For pre-operative fMRI, it is important to choose activation procedures that are appropriate tests of function in the area of brain to be resected.

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) provides measurements of specific brain metabolites. Metabolites that are detectable with ^{1}H MRS include *N*-acetylaspartate (NAA), choline (Cho), creatine (Cr), lactate, γ-aminobutyric acid (GABA) and glutamate. There is evidence that NAA is located primarily within neurones and precursor cells. Creatine and choline are found in both neurones and glia. Accurate definition of brain anatomy and the

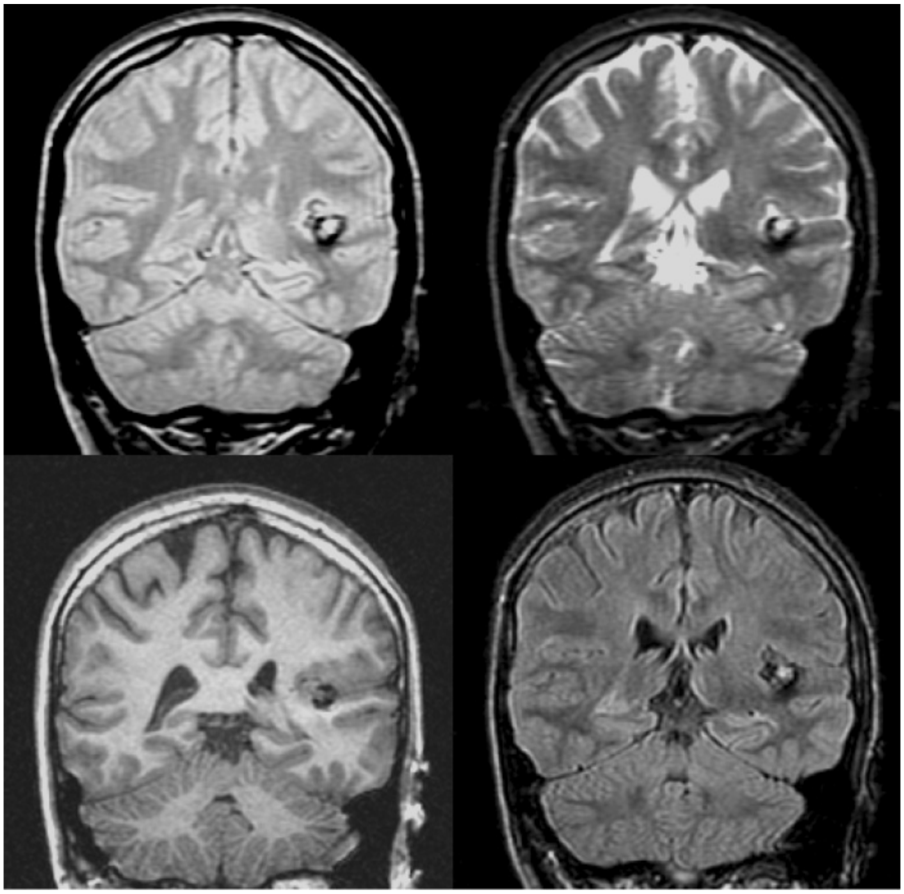

Figure 6.8 Cavernoma on the left (coronal 3.0 T MRI). Proton density (top L), T2-weighted (top R), IR_{prep} T1-weighted (low L), FLAIR (low R). The acquisitions demonstrate heterogeneous hyperintense signal caused by blood products in different stages of evolution, surrounded by a rim of low signal intensity from haemosiderin.

identification of structural abnormalities with MRI are necessary for the interpretation of MRS.

Single-photon emission computed tomography

Single-photon emission computed tomography (SPECT) allows measurements of regional cerebral blood flow changes in the areas affected by epileptic activity. Radioligands principally used in SPECT studies are ^{99m}Tc-hexamethyl-propylenamine oxime (^{99m}Tc-HMPAO) and technetium-^{99m}Tc-cysteinate dimer (ECD, bicisate). Currently available stabilized forms of ^{99m}Tc-HMPAO and ECD are stable i*n vitro* for several hours, whereas unstabilized ^{99m}Tc-HMPAO needs to reconstructed immediately before intravenous injection. Seventy-five per cent of ^{99m}Tc-HMPAO is extracted across the blood–brain barrier, reaching peak concentrations within 1 minute after injection. The images can then be acquired up to 6 hours after tracer injection. Both ictal and postictal SPECT studies should be performed during simultaneous video-EEG monitoring to determine the relationship between seizure onset and tracer injection. Interictal SPECT images serve as a reference baseline study for the interpretation of ictal images.

Ictal ^{99m}Tc-HMPAO SPECT is highly sensitive and specific in localizing seizure onset in intractable TLE. Correct localization of complex partial seizures may be achieved in over 90% of TLE patients. The use of subtraction ictal SPECT co-registered to MRI (SISCOM) improves the rate of localization. A characteristic pattern in temporal lobe seizures is an initial hyperperfusion of the temporal lobe, followed by medial temporal hyperperfusion and lateral temporal hypoperfusion. Postictal and interictal SPECT injections are easier to perform than ictal injections, but the images are more difficult to interpret and have lower sensitivity and specificity and are not clinically as useful as a stand-alone test.

Extratemporal seizures are often brief and it is therefore difficult to obtain an ictal recording. Accurate localization of an extratemporal seizure focus may be possible in 90% of the cases using the SISCOM technique. Ictal SPECT demonstrates ipsilateral frontal hyperperfusion in frontal lobe epilepsy. Activations may also be detected in the ipsilateral basal ganglia and contralateral cerebellum. The method provides additional information in patients with unrevealing EEG and MRI results, and can also be used to study the blood flow changes underlying specific clinical features observed in extratemporal seizures. Postictal and interictal SPECT is of very limited localizing value in extratemporal epilepsy.

Ictal SPECT provides a complementary method for localizing seizure foci in patients with intractable focal epilepsy evaluated for surgical treatment. The investigation may be particularly valuable in patients with normal MRI and presumed extratemporal seizures in order to generate a hypothesis that may then be tested with intracranial EEG recordings.

Positron emission tomography

^{18}*F-deoxyglucose*

Positron emission tomography (PET) maps cerebral glucose metabolism using ^{18}F-deoxyglucose (^{18}FDG). Interictally, PET shows areas of reduced glucose metabolism that usually include the seizure focus but are more extensive. Regional hypometabolism is best analysed with co-registration of PET scans to MRI. Voxel-based statisitical parametric mapping (SPM) has been shown to be useful in clinical evaluation of the data, and quantitative analysis with correction for partial volume effects further improves the accuracy of the method. The spatial resolution of quantitative ^{18}FDG-PET is superior to SPECT. Ictal ^{18}FDG-PET scans are difficult to obtain because cerebral uptake of ^{18}FDG occurs over 40 minutes after injection.

^{18}FDG-PET detects interictal glucose hypometabolism ipsilateral to the seizure focus in 60–90% of TLE patients. Unilateral, or asymmetric bilateral diffuse regional hypometabolism usually extends medially and laterally in the temporal lobe. ^{18}FDG-PET has some additional sensitivity over optimal volumetric MRI but does not provide clinically useful information if hippocampal atrophy is present. ^{18}FDG-PET is more useful lateralizing than localizing the epileptic focus. Unilateral focal temporal hypometabolism in ^{18}FDG-PET predicts a good outcome of surgery for TLE. Absence of unilateral hypometabolism, however, does not preclude a favourable outcome. Symmetric bilateral temporal hypometabolism is associated with higher incidence of postoperative seizures as are areas of severe extratemporal cortical, or thalamic hypometabolism.

^{18}FDG-PET has lower sensitivity for lateralization of epileptic foci in extratemporal epilepsies than in TLE. The areas of decreased glucose metabolism are also less frequently well-localized. Sixty per cent of the patients with frontal lobe epilepsy show regional hypometabolism in ^{18}FDG-PET, and a relevant underlying structural pathology is found on MRI in 90% of them. The area of hypometabolism may be either diffuse or widespread, or restricted to the co-localizing MRI lesion. In the majority of patients with frontal lobe epilepsy, however, ^{18}FDG-PET does not appear to provide additional clinically useful information.

In summary, the place of interictal ^{18}FDG-PET is in determining the lateralization of epileptic focus, especially in the presurgical assessment of patients where there is not good concordance between MRI, EEG, and other data, in order to generate a hypothesis to be tested with intracranial EEG recordings.

Medical treatment

Principles of treatment of newly diagnosed patients

The decision to initiate drug therapy has important implications for every person with epilepsy. In addition to its biological effects, therapy confers illness status, confirms the state of 'being epileptic', can affect self-esteem, social relationships, education and employment. The decision to treat depends essentially on a balance between the benefits and the drawbacks of therapy, and should be tailored to requirements of the individual patient. The benefits of therapy include the lower risk of recurrence of seizures, and thus of potential injury and even death, the psychological and social benefits of more security from seizures. The drawbacks of therapy include the potential drug side effects, the psychological and social effects, the cost and inconvenience. Chronic, long-term or subtle side effects are not easily detected, and weigh heavily on the decision to treat. One example is the potential adverse effect on learning in children, and partly because of this paediatricians initiate therapy less early than adult neurologists. The following factors influence the decision.

Diagnosis

It is essential to establish a firm diagnosis of epilepsy before therapy is started. This is not always easy, particularly in the early stages of epilepsy. There is almost no place at all for a 'trial of treatment' to clarify the diagnosis; it seldom does. A good first-hand witnessed account is essential, as diagnostic tests are often non-confirmatory. In practice, the misdiagnosis rate is quite high. For example, about 20% of all patients referred to a tertiary level epilepsy service have psychogenic attacks.

Risk of recurrence of seizure

The estimation of risk of seizure recurrence is obviously a key factor in deciding whether or not to initiate therapy. It is now generally accepted that about 50–80% of all patients who have a first unprovoked non-febrile seizure will have further attacks. The risk of recurrence is high initially and then falls over time. In a national UK study, the risk of a recurrence after the first seizure was 44% in the initial 6 months, 32% in the next 6 months and 17% in the second year. It follows also that the greater the elapsed time since the first attack, the less likely is subsequent recurrence (Figure 6.9). In many cases, by the time of presentation, seizures will have already recurred. In a hospital-based study from the UK, the median number of tonic–clonic seizures occurring before the diagnosis was made was 4 (range 1–36) and the median number of partial seizures was 6 (range 1–180).

If more than one spontaneous seizure has occurred, the risk of further attacks in the future without treatment is, in most clinical circumstances, over 80%, and generally speaking the more seizures that have occurred prior to therapy, the greater the risk of further attacks. The risk of recurrence is influenced by a number of factors:

- *Aetiology* The risk is greater in those with structural cerebral disease, and least in acute symptomatic seizures provoked by metabolic or drug and/or toxin exposure. The risk of recurrence of 'idiopathic' or 'cryptogenic' seizures is approximately 50%, and lower after actue symptomatic (provoked) seizures providing the provoking factor is removed.

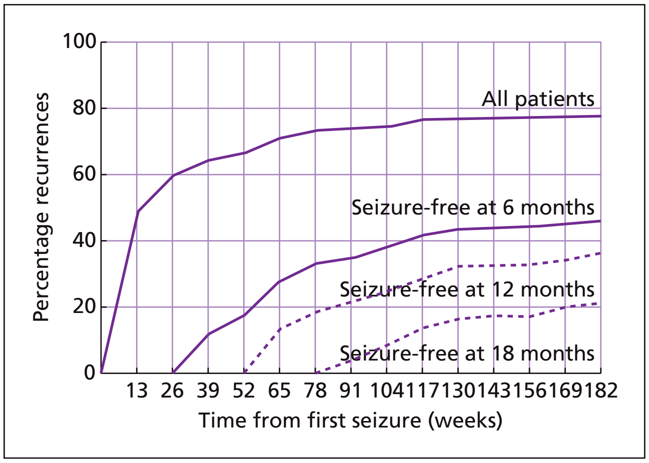

Figure 6.9 Actuarial percentage risk of recurrence after a first seizure (from the National General Practice Study of Epilepsy [NGPSE]). The lines show the risk of recurrence in all patients ($n = 564$) at the time of the first seizure, and then the subsequent risks for patients still seizure-free at 6, 12 and 18 months after the first seizure.

Table 6.15 Principles of antiepileptic drug treatment in patients with newly diagnosed epilepsy.

Aim for complete control without adverse-effects
Diagnosis of epileptic seizures should be unequivocal
Seizure type, syndrome and aetiology should be established
Baseline haematological and biochemical investigations should be performed prior to drug initiation
Use one drug at a time (monotherapy), at least initially
Initial titration should be to low maintenance doses
Further upward titration will depend on response and side-effects
If first drug fails, alternative monotherapies should be tried
Upward and downward titration should be in slow, stepped doses
Polytherapy should be used only if monotherapy will at least three first choice drugs has failed to control seizures
Patients should be fully counselled about goals, role, risk, outcome and logistics of drug treatment

- *EEG* Evidence in this area is contradictory. While there is consensus that the risk of recurrence is high if the first EEG shows spike and wave discharges, the predictive value of a normal EEG or an EEG with other types of abnormality after a single seizure – and if there is any predictive value – is slight.
- *Age* The risk of recurrence is somewhat greater in those under the age of 16 or over the age of 60 years, probably because of the confounding effect of aetiology.
- *Seizure type and syndrome* Partial seizures are more likely to recur than generalized seizures, again because of the confounding effect of aetiology. Children with most of the benign epilepsy syndromes (e.g. BECTS) have a few seizures only. In the other more severe childhood epilepsy syndromes, recurrent seizures are almost inevitable.

Type, timing and frequency of seizure

Some types of epileptic seizure often have a minimal impact on the quality of life; e.g. simple partial seizures, absence or sleep attacks. The benefits of treating such seizures, even if happening frequently, can be outweighed by the disadvantages. If the baseline seizure frequency is very low, the disadvantages of treatment can be unacceptably high. It would be unusual to treat a person having less than one seizure a year, especially if this was confined to sleep, or a minor or partial seizure.

A protocol for initial treatment

A protocol for the initial treatment in newly diagnosed patients is as follows (summarized in Table 6.15). Details of the available antiepileptic drugs are summarized in Tables 6.16–6.20:

1 Establish diagnosis. There is little place for a 'trial of treatment'. Investigation will usually involve EEG and neuroimaging, and other investigations as necessary. Neuro-imaging should be with MRI scanning in all patients with partial-onset epilepsy or epilepsy developing after the age of 15 without good explanation. The MRI must be of high quality, with T1-, T2-weighted and FLAIR sequences. Volumetric scanning is useful as this allows reformatting and quantitation.

2 Identify and counsel about precipitating factors – if these can be avoided, this occasionally obviates the need for drug therapy.

3 Decide upon the need for antiepileptic drug therapy. If therapy is needed, baseline biochemical and haematological parameters should be measured.

4 Advise about the goals, likely outcome, risks and logistics of therapy. Patients should be given clear instructions to seek immediate medical attention if signs of hypersensitivity or idiosyncratic drug reactions develop.

5 Start monotherapy with the chosen first-choice drug, initially at low doses, and titrating up slowly to a low maintenance dose. Emergency drug loading is seldom necessary except where status epilepticus threatens.

6 If seizures continue, titrate the dose upwards to higher maintenance dose levels (guided, where appropriate, by serum level monitoring). In about 60–70% of patients, these simple steps for initial therapy will result in complete seizure control.

7 In remaining patients, alternative monotherapy should be tried with another appropriate first-choice antiepileptic drug. The second drug should be introduced incrementally at suitable dose intervals, and the first drug then withdrawn in slow decremental steps. The second drug should be titrated first to low maintenance doses. Then, if seizures continue, the dose should be increased incrementally to maximal doses.

8 If the steps in (7) fail, a third alternative monotherapy should be tried in the same manner. If seizures continue, or recur after initial therapy with 1–3 drugs tried in monotherapy as above:

9 The diagnosis should be reassessed in patients with continuing attacks. It is not uncommon in this situation to find that the attacks do not have an epileptic basis. Investigation should be

Table 6.16 The range of antiepileptic drugs in current use.

Drug (year of introduction)	Putative mode(s) of action	Route(s) of elimination and metabolites	Main indication	Usual daily maintenance dose in adolescent and adults (mg)	Major safety issues or concerns
Acetazolamide (1952)	Carbonic, anhydrase inhibition	Renally excreted	Last resort broad spectrum drug	500–1000	Idiosyncratic rash; rarely Stevens–Johnson syndrome and toxic epidermal necrolysis; aplastic anaemia
Carbamazepine (1963)	Sodium channel inhibition	Hepatic metabolism; active metabolite	First line drug for partial and tonic-clonic seizures	400–1800	Idiosyncratic skin reactions; rarely, Stevens–Johnson syndrome; aplastic anaemia, hepatotoxicity
Clobazam (1986)	GABA augmentation	Hepatic metabolism; active metabolite	Broad spectrum adjuvant drug	10–30	Rarely, idiosyncratic rash
Clonazepam (1975)	GABA augmentation	Hepatic metabolism	Broad spectrum adjuvant drug	1–6	Rarely, idiosyncratic rash, thrombocytopenia
Diazepam (1965)	GABA augmentation	Hepatic metabolism; active metabolite	Emergency or rescue use only	N/A	Respiratory depression
Ethosuximide (1953)	Calcium channel modification	Hepatic metabolism; 25% excreted unchanged	Generalized absences only	500–1500	Rarely, idiosyncratic skin rash, Stevens–Johnson syndrome, aplastic anaemia
Felbamate (1993)	Glutamate reduction	Hepatic metabolism; active metabolites	Last resort broad spectrum drug	1800–3600	Hepatic failure, aplastic anaemia
Gabapentin (1993)	Calcium channel modulation	Not metabolized, urinary excretion unchanged	Second line drug in partial seizures	1800–3600	Paradoxical increase in seizures
Lamotrigine (1991)	Sodium channel inhibition; glutamate reduction	Hepatic metabolism by glucuronidation	Broad spectrum first line drug	100–400	Idiosyncratic skin rashes; rarely, Stevens–Johnson syndrome, toxic epidermal necrolysis, liver failure, aplastic anaemia, multi-organ failure
Levetiracetam (1999)	Synaptic vesicle protein modulation	Non-hepatic metabolism; renal excretion	Broad spectrum first line drug	750–4000	Behavioural problems
Lorazepam (1972)	GABA augmentation	Hepatic metabolism	Emergency or rescue use only	N/A	Respiratory depression
Phenobarbital (1912)	GABA augmentation	Hepatic metabolism; 25% excreted unchanged	Broad spectrum drug currently used as second line drug	30–180	Idiosyncratic rash; rarely, toxic epidermal necrolysis; hepatotoxicity; osteomalacia; Dupuytren contracture
Phenytoin (1938)	Sodium channel inhibition	Saturable hepatic metabolism	Of use in partial epilepsy	200–400	Idiosyncratic rash; rarely: peripheral neuropathy; Stevens–Johnson syndrome; Dupuytren contracture; hepatotoxicity; osteomalacia
Pregabalin (2004)	Calcium channel modulation	Not metabolized, excreted unchanged	Second line drug for partial seizures	100–600	Weight gain; rarely, increased seizures
Primidone (1952)	GABA augmentation	Hepatic metabolism	As for phenobarbital	500–1500	Idiosyncratic rash; rarely, agranulocytosis; thrombocytopenia; lupus-like syndrome
Oxcarbazepine (1990)	Sodium channel inhibition	Hepatic metabolism	First line drug for partial seizures	900–2400	Idiosyncratic rash; hyponatraemia
Tiagabine (1996)	GABA augmentation	Hepatic metabolism	Second line drug for partial seizures	30–45	Increased seizures; non-convulsive status
Topiramate (1995)	Glutamate reduction; sodium channel modulation; calcium channel modification	Mostly hepatic metabolism, with renal excretion	First line broad spectrum drug	75–400	Weight loss; kidney stones; impaired cognition
Valproate (1968)	GABA augmentation	Hepatic metabolism; active metabolites	First line drug for all generalized seizures and useful in partial seizures	400–2000	Teratogenicity; rarely, acute pancreatitis; hepatotoxicity; thrombocytopenia; encephalopathy; polycystic ovarian syndrome
Vigabatrin (1989)	GABA augmentation	Not metabolized 85% excreted unchanged	Very restricted use	1000–2000	Visual field defects, increased seizures
Zonisamide (1990)	Calcium channel inhibition	Hepatic metabolism; renal excretion	Second line drug for partial and generalized seizures	200–600	Skin rash; rarely, blood dyscrasias

Table 6.17 Drug options by epilepsy syndrome seen in adult practice (modified from NICE).

Epilepsy syndrome	First line drugs	Second line drugs	Other drugs	Drugs to be avoided (may worsen seizures)
Juvenile absence epilepsy	Lamotrigine Sodium valproate Ethosuximide	Levetiracetam Topiramate	Clonazepam Clobazam	Carbamazepine Phenytoin Oxcarbazepine Tiagabine Vigabatrin
Juvenile myoclonic epilepsy	Lamotrigine Sodium valproate Levetiracetam Topiramate	Clobazam Clonazepam	Acetazolamide	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Generalized tonic–clonic seizures only	Carbamazepine Lamotrigine Sodium valproate Levetiracetam Topiramate	Clobazam Clonazepam Oxcarbazepine Zonisamide	Acetazolamide Phenobarbital Phenytoin Primidone	Tiagabine Vigabatrin
Focal epilepsies: cryptogenic, symptomatic	Carbamazepine Lamotrigine Oxcarbazepine Levetiracetam Sodium valproate Topiramate	Clobazam Gabapentin Levetiracetam Phenytoin Pregabalin Tiagabine Topiramate Zonisamide	Acetazolamide Clonazepam Gabapentin Phenobarbital Primidone	
Benign epilepsy with centrotemporal spikes	Carbamazepine Lamotrigine Oxcarbazepine Sodium valproate			
Benign epilepsy with occipital paroxysms	Carbamazepine Lamotrigine Oxcarbazepine Sodium valproate	Levetiracetam Topiramate		

Table 6.18 Drug options by seizure type (modified from NICE).

Seizure type	First line drugs	Second line drugs	Other drugs that may be considered	Drugs to be avoided (may worsen seizures)
Generalized tonic–clonic	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate Topiramate	Clobazam Clonazepam	Acetazolamide Phenobarbital Phenytoin	Tiagabine Vigabatrin
Absence	Ethosuximide Lamotrigine Sodium valproate	Clobazam Clonazepam Topiramate	Phenobarbital	Carbamazepine Gabapentin Oxcarbazepine Pregabalin Tiagabine Vigabatrin

Continued on p. 224

Table 6.18 *Continued*

Seizure type	First line drugs	Second line drugs	Other drugs that may be considered	Drugs to be avoided (may worsen seizures)
Myoclonic	Sodium valproate Topiramate Levetiracetam	Clobazam Clonazepam Lamotrigine Piracetam Zonisamide		Carbamazepine Gabapentin Oxcarbazepine Pregabalin Tiagabine Vigabatrin
Tonic	Lamotrigine Sodium valproate	Clobazam Clonazepam Levetiracetam Topiramate	Acetazolamide Phenobarbital Phenytoin	Carbamazepine Oxcarbazepine
Atonic	Lamotrigine Sodium valproate	Clobazam Clonazepam Levetiracetam Topiramate	Acetazolamide Phenobarbital	Carbamazepine Oxcarbazepine Phenytoin
Focal with/without secondary generalization	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate Topiramate	Clobazam Gabapentin Pregabalin Tiagabine Zonisamide	Acetazolamide Clonazepam Phenobarbital Phenytoin	

Table 6.19 Usual dosing regimens and fastest routine incremental and decremental rates in adults.

	Initial dose (mg/day)	Drug initiation: usual dose increment (mg/day) stepped up every 2 weeks	Usual maintenance dose on monotherapy (mg/day)	Usual maximum dose in monotherapy (mg/day)	Dosing intervals (per day)	Drug reduction: usual dose decrement (mg/day) stepped down every 4 weeks	Maintenance doses can be different when given as co-medication
Carbamazepine*	100	100–200	400–1600	2000	2	200	Yes
Clobazam	10	10	10–30	30	1–2	10	
Clonazepam	0.25	0.25–0.5	0.5–4		1–2	1	
Ethosuximide	250	250	750–1500		2–3	250	Yes
Gabapentin	300–400	300–400	900–2400	3200	2–3	300	
Lamotrigine	12.5–25	25–100	100–400	600	2	100	Yes
Levetiracetam	125–250	250–500	500–1500	4000	2	250	
Oxcarbazepine	600	300	600–2400	3000	2	300	Yes
Phenobarbital	30	30–60	60–120	180	1–2	30	Yes
Phenytoin	200	25–100	200–400	450	1–2	50	Yes
Pregabalin	50	50	150–600	600	2	50	
Primidone	62.5–125	125–250	250–1000	1500	1–2	125	Yes
Tiagabine	4–5	4–15	15–16	56	2–3	5	Yes
Topiramate	25–50	50–100	100–300	600	2	50	Yes
Valproate	200–500	200–500	600–1500	3000	2–3	200	Yes
Vigabatrin	1000	500	1000–2000	4000	2	500	
Zonisamide	50	50	200–400	600	1–2	50	Yes

Values in this table are based on the authors' own practice, and may vary from those published elsewhere.

*Values are for the slow release formulation, which is the formulation of choice, particularly at high doses.

Table 6.20 Some pharmacokinetic parameters of antiepileptic drugs.

	Oral Bio-availability (%)	Time to peak level (hours)	Metabolism	Half-life† (hours)	Protein binding (%)	Active metabolite	Drug interactions	Phase 1 reactions	Phase 2 reactions	P450 enzymes identified in the phase 1 reactions^{3}
Carbamazepine	75–85	4–8	Hepatic	5–26^{5}	75	CBZ-epoxide	**	Epoxidation, hydroxylation	Conjugation	CYP3A4 CYP 2C8 CYP 1A2
Clobazam	90	1–4	Hepatic	10–77 (50^{1})	83	*N*-desmethyl clobazam	*	Demethylation, hydroxylation	Conjugation	CYP 3A4
Clonazepam	80	1–4	Hepatic	20–80	86	None	*	Reduction, hydroxylation	Acetylation	
Ethosuximide	<100	<4	Hepatic	30–60^{5}	<10	None	**	Oxidation	Conjugation	
Gabapentin	<65^{6}	2–3	None	5–7	None	None	None	Renal excretion without metabolism		
Lamotrigine	<100	1–3	Hepatic	12–60^{5}	55	None	**	No phase 1 reaction	Conjugation	–
Levetiracetam	<100	1–2	Non-hepatic	6–8	None	None	None	Hydrolysis by non-hepatic enzymes		
Oxcarbazepine	<100	4–6	Hepatic	8–10^{1,5}	38^{1}	MHD	**	Reduction	Conjunction	
Phenobarbital	80–100	1–3	Hepatic	75–120^{5}	45–60	None	**	Oxidation, glucosidation, hydroxylation	Conjunction	CYP 2C9 CYP 2C19 CYP 2E1
Phenytoin	95	4–12	Hepatic	7–42^{2,5}	85–95	None	**	Oxidation, glucosidation, hydroxylation	Conjunction	CYP 2C9 CYP 2C19 CYP 3A4
Pregabalin	90	1	None	6	None	None	None	Renal excretion without metabolism		

Continued on p. 226

Table 6.20 *Continued*

	Oral Bio-availability (%)	Time to peak level (hours)	Metabolism	Half-life† (hours)	Protein binding (%)	Active metabolite	Drug interactions	Phase 1 reactions	Phase 2 reactions	P450 enzymes identified in the phase 1 reactions^3
Primidone	<100	3	Hepatic	5–18^5 (75–120^1)	25	Phenobarbital	**	Transformation to phenobarbital and a phenylethyl deriviative, then metabolized as per phenobarbital		
Tiagabine	<96	1–2^3	Hepatic	5–9^5	96	None	**	Oxidation	Conjunction	CYP 3A4
Topiramate	<100	2–4	Hepatic	19–25^5	15	None	**	Hydroxylation, hydrolysis	Conjunction	
Valproate	<100	0.5–8^4	Hepatic	12–17^5	85–95	None	**	Oxidation, hydroxylation, epoxidation, reduction^2	Conjugation	CYP 4B1 CYP 2C9 CYP 2A6 CYP 2B6 CYP 2C19
Vigabatrin	<100	0.5–2	None	4–7	None	None	None	Renal excretion without metabolism		
Zonisamide	<100	2–4	Hepatic	49–69^5	30–60	None	**	Acetylation, reduction	Conjugation	CYP 3A4

1 Value for active metabolite.

2 Phenytoin has non-linear kinetics, and so half-life can increase at higher doses.

3 Absorption of tiagabine is markedly slowed by food, and it is recommended that the drug is taken at the end of meals.

4 The time to peak concentration varies according to formulation (0.5–2 hours for normal formulation, 3–8 hours for enteric coated).

5 Half-life varies with co-medication.

6 Absorption of gabapentin is by a saturable active transport system, and rate will depend on capacity of the system.

* Minor interactions common, but not usually of much clinical relevance.

** Many interactions, frequently of clinical relevance and many require dose modification.

† Half-life in healthy adult.

considered to exclude the possibility of a progressive lesion. The possibility of poor compliance should be explored.

10 Alternative monotherapies or polytherapy should be considered.

11 The patient should be referred for specialist advice.

Treatment protocol for patients with chronic epilepsy

When first seeing a patient with chronic uncontrolled epilepsy, a two-stage procedure should be adopted. First, an assessment of diagnosis and previous treatment history should be made. As a second step, a treatment plan should be devised (Table 6.21).

Assessment

The steps in the assessment are summarized in Table 6.21. The review of previous treatment history is an absolutely essential step, often omitted. The response to a drug is generally speaking relatively consistent over time. Find out which drugs have been previously tried, what was the response (effectiveness, side effects), what was the maximum dose and why the drug was withdrawn.

Treatment plan

A treatment plan (schedule) should be formed on the basis of this assessment. The plan should take the form of a stepwise series of treatment trials, each to be tried in turn (if the previous trial fails to meet the targeted level of seizure control). The treatment plan is ideally devised to trial each available antiepileptic in turn, in a reasonable dosage, singly or as two-drug therapy (or, more rarely, three-drug combinations). This will involve deciding which drugs to introduce, which drugs to withdraw and which drugs to retain. Decisions will also be needed about the duration of each treatment trial. There is often nihilistic inertia in much of the treatment of chronic epilepsy which should be resisted, and an active and logical approach to therapy can prove very successful.

Choice of drug to introduce or retain

Generally, these should be drugs that are appropriate for the seizure type and that have either not been previously used in optimal doses or that have been used and did prove helpful (Tables 6.16–6.20). Rational choices depend on a well-documented history of previous drug therapy. Other factors are also important – and therapy where possible should be tailored to individual requirements; such factors include co-morbidities, co-medication, obesity, gender, lifestyle, age and renal or hepatic disease.

Choice of drug to withdraw

These should be drugs that have been given an adequate trial at optimal doses and that were either ineffective or caused unacceptable side effects. There is obviously little point in continuing a drug that has had little effect, yet it is remarkable how often this is done.

Duration of treatment trial

This will depend on the baseline seizure rate. The trial should be long enough to have differentiated the effect of therapy from that of chance fluctuations in seizures.

Trial of therapy

It is usual to maintain aim for therapy with either one or two suitable antiepileptic drugs. If drugs are being withdrawn, it is wise to maintain one drug as an 'anchor' to cover the withdrawal period.

Drug withdrawal

Drug withdrawal needs care. The withdrawal, or sudden reduction in dose, of antiepileptics can result in a severe worsening of seizures or in status epilepticus – even if the withdrawn drug was apparently not contributing much to seizure control. Only one drug should be withdrawn at a time. If the withdrawal period is likely to be difficult, the dangers can be reduced by covering the withdrawal with a benzodiazepine drug (usually clobazam 10 mg/day), given during the phase of active withdrawal.

Drug addition

New drugs added to a regimen should also be introduced slowly, at least in the routine clinical situation. This results in better tolerability, and too fast an introduction of these drugs will almost invariably result in side effects. It is usual to aim initially for a low maintenance dose, but in severe epilepsy higher doses are often required.

Limits of therapy

Drug therapy will fail in about 10–20% of patients developing epilepsy. In this situation, the epilepsy can be categorized as 'intractable' and the goal of therapy changes to defining the best compromise between inadequate seizure control and drug-induced side effects. Individual patients will take very different views about where to strike this balance. Intractability is inevitably

Table 6.21 Principles of antiepileptic drug treatment in patients with chronic epilepsy.

Assessment
Review diagnosis and aetiology (history, EEG, imaging)
Classify seizures and syndrome
Review adherence to prescription
Review drug history:
  Which drugs were useful in the past
  Which drugs were not useful in the past
  Which drugs have not been used in the past
  (also dosage, length of therapy, reasons for discontinuation)
Review precipitants and non-pharmacological factors

Treatment plan
Document proposed sequence of drug 'trials'
Decide what background medication to continue
Decide upon the sequence of drug additions and withdrawals
Decide the duration of drug 'trials'
Decide when to do serum level monitoring
Consider surgical therapy
Consider non-pharmacological measures (e.g. lifestyle, alternative therapy)
Recognize the limitations of therapy
Provide information on above to patients

an arbitrary decision. There are over 10 first line antiepileptic drugs, and far more combinations (with 10 first line antiepileptic drugs there are 45 different two-drug and 36 different three-drug combinations). All combinations cannot therefore be tried.

Monotherapy versus combination therapy

Single-drug therapy will provide optimal seizure control in about 70% of all patients with epilepsy, and should be chosen whenever possible. The advantages of monotherapy are:

- Better tolerability and fewer side effects;
- Simpler and less intrusive regimens;
- Better compliance; and
- No potential for pharmacokinetic or pharmacodynamic interactions with other antiepileptic drugs.

Combination therapy is needed in about 20% of all those developing epilepsy, and in a higher proportion of those with epilepsy that has remained uncontrolled in spite of initial monotherapy (chronic active epilepsy). The prognosis for seizure control in these patients, even on combination therapy, is far less good. Nevertheless, skilful combination therapy can make a substantial difference by optimizing control of the epilepsy and minimizing the side effects of treatment. The choice of drugs in combination has not been satisfactorily studied. It has been proposed, but without any substantial supporting evidence, that mixing drugs with differing modes of action has a synergistic effect. Patients need to be advised carefully about the implications of polytherapy in terms of drug interactions, teratogenesis and potential pharmacodynamic effects.

Role of antiepileptic drug level measurements

The measurement of drug levels of some antiepileptic drugs is helpful for a number of reasons – and in chronic refractory patients these include assessing optimal doses, assessing toxicity and side effects, assessing interactions with other drugs and compliance. The levels of phenytoin should be regularly measured due to the non-linear kinetics of this drug.

Patient information

All treatment is a balance between benefits (seizure control) and risk (e.g. side effects) and it is important to tell patients of the risks of therapy so that an informed decision can be made. Written information is generally better than simple verbal instruction. Consent to therapy must be informed and patients should be given enough time to discuss and explore the various treatment options.

Treatment of patients with epilepsy in remission

Epilepsy can be said to be in remission when seizures have not occurred over long time periods (conventionally 2 or 5 years). Some 70–80% of patients will be in remission at some point after the initiation of therapy. Many cases of untreated epilepsy also remit and in the long-term at least 50% of patients are in remission and off medication. The clinical management of ongoing therapy in patients in remission is usefully straightforward. Drug doses should be minimized, and it is usually possible to avoid major adverse effects. In most cases, little medical input is required with appropriate care provided at primary care level and annual visits to the specialist. The seizure type, epilepsy syndrome, aetiology, investigations and previous treatment should be recorded. Routine haematological or biochemical checks are recommended on an annual basis in an asymptomatic individual. Enquiry should be made of long-term side-effects (e.g. bone disease in post-menopausal women) and counselling about issues such as pregnancy made where appropriate. At some point, the calm of this ideal situation is likely to be disturbed by the question of discontinuation of therapy.

Table 6.22 Some factors that increase the risk of seizure recurrence after withdrawal of therapy in patients with epilepsy in remission.

Short duration of seizure freedom prior to drug withdrawal
Age above 16 years
History of myoclonic seizures or secondarily generalized seizures
History of multiple seizure types
Certain epilepsy syndromes (e.g. juvenile myoclonic epilepsy, childhood encephalopathies)
Symptomatic epilepsy
Prolonged period of active epilepsy before achieving seizure control
History of seizures after treatment was initiated
Seizure control requiring multiple drug therapy
EEG showing generalized spike-wave discharges
Presence of learning disability or associated neurological handicaps

Discontinuation of drug therapy

It is often difficult to decide when (if ever) to discontinue drug treatment. The decision should be made by a specialist who is able to provide an estimate of the risk of reactivation of the epilepsy. This risk is influenced by the factors listed in Table 6.22; but it must be stressed that withdrawal is never entirely risk free. The decision whether or not to withdraw therapy will depend on the level of risk the patient is prepared to accept.

Probability of remaining seizure free after drug withdrawal

The best information comes from the Medical Research Council (MRC) antiepileptic drug withdrawal study, which included 1013 patients who had been seizure free for 2 years or more (Figure 6.10). Within 2 years of starting drug withdrawal 59% remained seizure free (compared to 79% of those who opted to stay on therapy). Other studies have had essentially similar findings.

Seizure-free period

The longer the patient is seizure free, the less is the chance of relapse. The overall risk of relapse after drug withdrawal, for instance, after a 5-year seizure-free period of is under 10%.

Duration of active epilepsy

This is probably an under-studied factor. One has a strong impression that the shorter the history of active seizures (i.e. the duration of time from the onset of epilepsy to the onset of remission), the less is the risk of relapse.

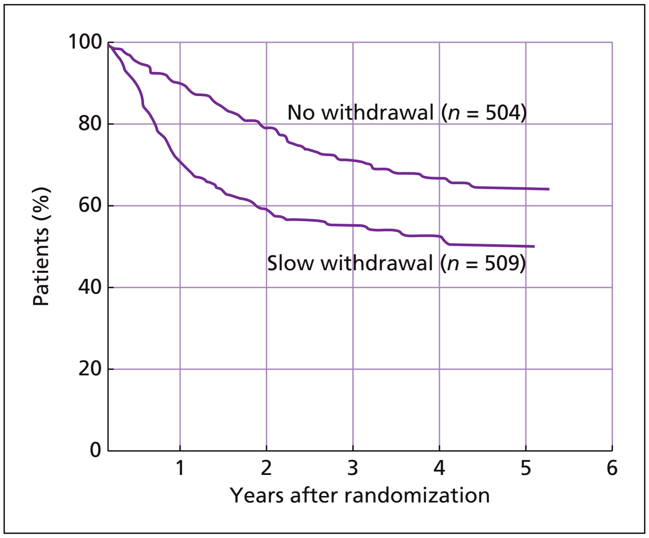

Figure 6.10 Medical Research Council (MRC) drug withdrawal study. Actuarial percentage of patients seizure-free amongst those randomized to continuing or to slow withdrawal of antiepileptic drugs. A study of 1013 patients who were seizure-free for 2 years or more. Two years after randomization, 78% of those who continued treatment and 59% of those who withdrew antiepileptic drugs were seizure-free.

Type and severity of epilepsy

The type of epilepsy and its aetiology are important influences on prognosis. The presence of symptomatic epilepsy, secondarily generalized or myoclonic seizures, neurological deficit or learning disability greatly lessen the chance of remission, and also increase the chances of recurrence should remission occur. The higher the number of seizures prior to remission, the greater the number of drugs being taken to control the seizures and the presence of two or more seizure types (a surrogate for severity of epilepsy) all increase the risk of relapse.

EEG

The persistence of spike-wave in those with IGE is the most useful prognostic EEG feature, indicating a higher chance of relapse. Other EEG abnormalities have no great prognostic utility, and the presence of focal spikes or changes to EEG background in adults are of little help in estimating the chances of remission or relapse after drug withdrawal.

Age

There is no clear overall relationship between age and the risk of relapse, although there are age-specific syndromes that have specific prognostic patterns. There is a low chance of relapse in the benign epilepsies of childhood or in generalized absence epilepsy. These data simply emphasize the obvious point that the over-riding determinant of prognosis is the type and aetiology of epilepsy.

How to withdraw therapy – the importance of slow reduction

When a decision to withdraw therapy is made, the drugs should be discontinued slowly one at a time. Fifty per cent of patients who are going to experience seizure recurrence on withdrawal do so during the reduction phase, and 25% in the first 6 months after withdrawal; this should be explained carefully to the patient, and driving restrictions should be applied during the withdrawal period and the subsequent 6 months.

The fastest recommended rates of withdrawal are given in Table 6.19, although in many instances there is no need to proceed so rapidly. In general terms, the slower the withdrawal, the less likely are seizures to recur. If seizures do recur, the drug should be immediately restarted at the dosage that controlled the attacks. About 10% of patients will not regain full remission even if the drug is replaced at the dosage that previously resulted in long remission. Why this should be the case is unclear, but in some patients at least, it seems that recurrence alters subsequent seizure risk.

Management of epilepsy in learning disability

Definition

Learning disability is a descriptive diagnosis or concept, not a disease or illness. Learning disability is defined as a composite of:

1 Deficiency in learning with an IQ of less than 70 (i.e. 2 standard deviation below the mean);

2 Difficulties with daily living skills; and

3 An onset within the developmental period (less than 18 years of age).

It does not infer a particular aetiology. Social functioning is an integral part of the diagnosis. It is different from mental illness; a person with learning disability can also develop mental illness. As a concept, it is also different from learning difficulties, which generally refers to specific learning problems (e.g. dyslexia), rather than a global impairment or intellect and function, although some ambiguity does exist in the use of the terms.

Prevalence of epilepsy in people with learning disability

People with learning disabilities are 30 times more likely to experience seizures than the general population. In most cases, both the cognitive difficulties and the seizures represent overt symptoms of the underlying pathology. The risk of epilepsy increases with more significant intellectual disabilities and additional motor and sensory impairments. Prevalence of epilepsy in people with severe learning disabilities and additional impairments ranges from 50 to 75%. The mortality ratio of people with learning disabilities and epilepsy is also higher than that of people with learning disabilities alone.

Assessment

The evaluation of epilepsy in people with learning disabilities is compounded by recollection and communication difficulties, coexistence of mental illness and by related problems that may mimic epileptic seizures.

Communication difficulties –'management by proxy'

People with learning disabilities and epilepsy tend to have consistently poorer adaptive and social skills and additional speech difficulties than people with intellectual disabilities alone. In this population, it is common to make a diagnosis and decisions about treatment based on carers' reports, a witness report from a carer or family member is common, a report from the individual is less so. Thus, history and management will commonly progress through another – 'management by proxy'. The degree of this will increase as the individual's communicative skills decrease. This is problematic, as people with learning disability often rely on paid care staff. Even though the content of concerns was found to be similar between families, care staff and clinicians, care staff showed the lowest degree of concern with poorest interrater reliability of all three groups, reflecting the level of emotional involvement with the client.

Psychiatric co-morbidity – 'diagnostic overshadowing'

People with learning disability and epilepsy are twice as likely to experience mental health problems, particularly affective disorders, than their peers without epilepsy. 'Diagnostic overshadowing' is common with a person's presenting symptoms put down to their learning disability, rather than seeking another, potentially treatable cause. Is the observed strange behaviour caused by epilepsy, mental illness (i.e. depression, psychosis related or unrelated to epilepsy), physical ailment (i.e. pain, deterioration in vision), an attempt at communication, a response to a stressful situation (i.e. change in carers, bereavement) or a side effect of a drug? People with learning disabilities can experience difficulties recognizing or communicating their internal experiences and therefore it is particularly important for this group that those around them survey all factors potentially implicated in behavioural change, e.g. antiepileptic drug intoxication.

With an increase in prevalence of nearly all forms of psychiatric disorders, people with learning disability and additional epilepsy are further socially disadvantaged with having a potentially life-threatening illness causing accidents, head injuries resulting in further brain damage and dependency on others. They often have less effective and cruder coping mechanisms, which can lead to difficulties in the diagnostic and treatment process:

- Non-epileptic attack disorders are more common in people with learning disability who have limited communication skills to express emotional conflicts;
- Self-induced seizures can be stress-avoidance mechanisms with pleasurable auras experienced in photosensitive patients, or providing a sense of control over the unpredictable epilepsies;
- Increased aggression is often reported, when seizures are reduced, either because of complex electrophysiological interactions ('forced normalization'), or less seizure-related sedation and, thus, greater awareness mixed with limited communication skills and ways to express frustration.

Behaviour or seizure

Seizures are paroxysmal episodes of abnormal behaviour. A generalized tonic–clonic convulsion is well defined and does not mimic many other conditions. Other seizure types, however, are less well defined and are dependent on the verbal description of the individual and witnesses for a diagnosis. Patterns of behaviour seen in complex partial seizures, particularly when there are associated ictal or post-ictal automatisms, can be difficult to differentiate from psychiatric disturbances or from non-epileptic attack disorders. Differentiating these in people with learning disability is further complicated by communication issues and the high prevalence of repetitive episodes of manneristic or stereotyped behaviours and motor disorders in this population.

It is not entirely clear how epilepsy is related to challenging behaviour. The results of studies have been at times contradictory, with some finding a relationship and others not. This is perhaps not surprising considering the wide variety of aetiologies and syndromes encompassed under the general umbrella of epilepsy and the fact that it is usually associated with additional impairments. There is a complex relationship between poor impulse control and people with learning disability and epilepsy, in particular arising from the frontal lobe. These people have been found to be more at risk of displaying challenging behaviour or episodic rage and aggression, which appears to be involuntary, has features of frontal lobe seizures and most likely is brought about by frontal lobe dysfunction.

Diagnostic difficulties

People with learning disabilities often have difficulties complying with medical procedures. Good planning and communication between the person and staff, carers and/or relatives is important to increase the chance of tolerating an EEG and/or MRI or any other tests. Even though people with learning disability often have diffuse brain abnormalities, and thus are poor candidates for resective curative surgery, both MRI and EEG can provide important diagnostic clarification and prognostic information. People with learning disabilities are often under-investigated and epilepsy often undiagnosed because of therapeutic nihilism on behalf of some doctors as well as management-by-proxy disproportionately carried out by poorly paid people with little understanding of the complexities of people with learning disabilities or carers from a very strong social background and little appreciation of health issues.

Treatment

As for all those with epilepsy, antiepileptic medication constitutes the first line of treatment. However, seizures remain poorly controlled for approximately 68% of clients with learning disabilities, despite the fact that around 40% regularly take more than one antiepileptic drug.

There is little evidence-based prescribing in people with learning disability and epilepsy who are usually excluded from most regulatory antiepileptic drug trials.

The majority of data on pharmacological studies comes from add-on open non-randomized design, usually with the novel antiepileptic drugs. Trials using open non-controlled methodology in populations with learning disability and refractory epilepsy have shown a 50% reduction in seizures in 33% of patients at 3 months follow-up on vigabatrin, with a reduction in this response by one-third at 5-year follow-up. A similar methodology using lamotrigine in a childhood population showed a

50% improvement in seizure control in 74% of children, with an associated improvement in quality of life using clinical judgement.

There are few randomized controlled trials, mainly focusing on the difficult to define epileptic syndrome of Lennox–Gastaut, which is strongly associated with learning disability. Both lamotrigine and topiramate led to significant reduction in atonic (drop) attacks and improvement in global health or reduction in seizure severity as assessed by parents. In West's syndrome, an impressive efficacy for vigabatrin was shown in both open and a limited placebo-controlled trials.

For the majority of people, we therefore apply knowledge on interventions gained in the general population to this special population, but the validity of this approach in this population remains unproven.

Seizure reduction, although still the prime aim of epilepsy treatment, should not be the only parameter by which the success of interventions can be assessed. Broader quality of life issues should be considered to evaluate the impact of epilepsy on an individual. This would seem particularly important in this already disadvantaged group, for whom freedom from seizure can also be very elusive. The UK government's 2001 White Paper emphasizes the need to involve the person with learning disabilities and to devise individually planned care. It seems vital therefore that we consider the individual's own concerns about their epilepsy if we are to develop more effective, broader treatments enabling people with learning disability who also have epilepsy to achieve their aspirations in life unimpeded by their epilepsy.

Antiepileptic drug treatment

Currently available antiepileptic drugs are presented in alphabetical order. Tables 6.16–6.20 comprise a summary of clinical, pharmacological and pharmacokinetic properties for each drug.

Acetazolamide

Acetazolamide, a carbonic anhydrase inhibitor, is primarily used in ophthalmology but can also be used in epilepsy. It is a broad-spectrum antiepileptic drug but it is used mainly in seizure disorders in the paediatric age group. In the adult population, it can be useful for intermittent use in catamenial epilepsy. One caveat is that many responders develop tolerance to its antiepileptic action if used continuously. Common side effects include paresthesia of extremities, alterations of taste, nausea and vomiting, diarrhoea, athralgia, loss of appetite, dizziness, fatigue, irritability, thirst and polyuria. Very rarely, rashes including Stevens–Johnson syndrome and toxic epidermal necrolysis may occur. As a carbonic anhydrase inhibitor, acetazolamide is associated with an increased risk of kidney stones. Patients should be advised to increase fluid intake to decrease this risk. Its main clinical relevant interaction is with carbamazepine as acetazolamide may increase its levels.

Benzodiazepines

Benzodiazepines are useful in epilepsy as both a rescue medication for serial seizures or prolonged seizures as well as for long-term treatment. Benzodiazepines such as diazepam, midazolam or lorazepam are not well suited for chronic oral treatment except as a last resort; however, they are useful in the emergency treatment of status epilepticus, serial or prolonged seizures. Clobazam and clonazepam are better suited for long-term treatment. Clobazam, a 1,5 benzodiazepine, may be very useful as an add-on for patients with refractory seizures, either partial or generalized, and may produce long-lasting seizure freedom in up to 30% of patients. Clonazepam can also be used, particularly in myoclonic seizures, but tends to be less well-tolerated. The main disadvantages of benzodiazepines are sedation, tolerance and the tendency to cause problems on withdrawal. Hypersensitivity reactions do not usually occur with benzodiazepines. Nevertheless, depression, fatigue or irritability may develop. Benzodiazepines are relatively devoid of clinically significant interactions.

Carbamazepine

Carbamazepine, an iminodibenzyl, is a first line drug for initial treatment of partial seizures and tonic–clonic seizures. Carbamazepine is a potent auto-inducer and must be started at a low dose to keep development of transient neurotoxicity at a minimum. The dose can be increased every 1–2 weeks to a maintenance level that controls the seizures. Even when taking this cautious approach, some patients may experience diplopia, nausea, dizziness or headache on initiation of therapy, although these effects are usually transient. Common side effects, apart from these, include drowsiness, ataxia, confusion and agitation (particularly in the elderly), hyponatraemia, neutropenia, idiosyncratic skin rashes. Very rare side effects include hepatitis, Stevens–Johnson syndrome, toxic epidermal necrolysis and cardiac conduction disturbances. Fluid retention may limit the use of carbamazepine in the elderly or those with cardiac failure. In addition, carbamazepine may aggravate bradycardia in patients with heart disease. Hyponatremia seen with carbamazepine is rarely symptomatic but occasionally leads to confusion, peripheral oedema and an increase in the number of seizures. The associated neutropenia does not usually cause any clinical manifestations. Controlled release preparations are preferable as they reduce toxicity associated with peak plasma concentrations of the drug. Carbamazepine, as an enzyme inducer, reduces the effectiveness of several drugs, such as oral contraceptives, steroids, haloperidol, antineoplastic drugs, antihypertensive drugs, tricyclic antidepressants, antipsychotic drugs, theophylline and warfarin. Conversely, other drugs inhibit its metabolism which may result in neurotoxicity; these include cimetidine, clarithromycin, dextropropoxyphene, diltiazem, erythromycin, imidazole antifungal drugs, isoniazid, tricyclic antidepressants, antipsychotic drugs, verapamil and viloxazine. Interactions of carbamazepine with other antiepileptic drugs are also common. Carbamazepine increases the clearance particularly of ethosuximide, sodium valproate, topiramate and lamotrigine. Inhibition or enzyme induction is seen with phenobarbital, phenytoin or primidone with usually small but unpredictable changes in the plasma concentrations of these drugs.

Ethosuximide

Ethosuximide, a succinimide, is a first line drug for the treatment of generalized absence seizures in children and young adults. It is not generally effective for other seizures types. The most important side effects are sedation, headaches, malaise, nausea, vomiting, abdominal pain and anorexia. Very rarely, it can cause psychotic episodes with paranoid ideation, aplastic anaemia, systemic lupus erythematosus and Stevens–Johnson syndrome. Ethosuximide-induced headache and abdominal pain can be severe in individual patients. Ethosuximide does not inhibit or induce the metabolism of other drugs but its clearance is reduced by valproate.

Felbamate

Felbamate, a dicarbamate, is an effective broad-spectrum drug particularly useful in refractory partial epilepsy and it was the first antiepileptic drug to have shown efficacy as add-on treatment in refractory Lennox–Gastaut syndrome. Its use is currently restricted to very refractory cases for safety reasons as it has been associated with an idiosyncratic reaction leading to aplastic anaemia or hepatotoxicity. These rare but often fatal reactions affect about 1/4000 people exposed. Felbamate is not currently licensed in the UK but can be obtained for selected cases on a named-patient basis. It interacts with many drugs and this needs to be taken into consideration when using felbamate.

Gabapentin

Gabapentin, an amino acid, is a mild antiepileptic drug occasionally useful as add-on treatment of partial seizures. It is not effective for any other seizure type. Its major indication currently is an analgesic for chronic neuropathic pain. Side effects of gabapentin include nausea, vomiting, peripheral oedema, dizziness, drowsiness, ataxia, tremor, asthenia, emotional lability, weight gain, dysarthria and diplopia. Rare side effects include pancreatitis, depression, psychosis, headache, myalgia and urinary incontinence; hepatitis, jaundice, movement disorders, thrombocytopenia and acute renal failure. Gabapentin is devoid of interaction and this is one of the few advantages of this drug.

Lamotrigine

Lamotrigine, a triazine, is a first line drug for partial and generalized seizures. It is a broad-spectrum drug but may occasionally exacerbate myoclonic seizures particularly as part of severe myoclonic epilepsy of infancy. The initiation of lamotrigine therapy should be at a very low dosage with a slow upward titration to decrease the risk of the development of skin rash, which is one of the most common and important side effects. The rash may be severe and lead to Stevens–Johnson syndrome in some rare cases, particularly if the medication is not stopped promptly. Other side effects include nausea, fatigue, dizziness, insomnia, tremor, agitation, confusion, hallucinations and blood disorders (including leucopenia, thrombocytopenia, pancytopenia). Lamotrigine has the potential for interaction. The elimination of lamotrigine is accelerated by enzyme-inducing antiepileptic drugs, such as carbamazepine, phenytoin and phenobarbital, and inhibited by valproate. Therefore, if lamotrigine is used as an add-on then dose and titration schedule needs to be adjusted according to the concomitant medication. In women, lamotrigine levels may be reduced, occasionally dramatically, with the use of the combined contraceptive pill or during pregnancy and dose adjustments may be necessary to avoid breakthrough seizures.

Levetiracetam

Levetiracetam, a pyridoline, is a broad-spectrum first line medication for partial and generalized seizures which is well tolerated overall. The most frequent side effects encountered in clinical practice are lethargy, irritability, ataxia, nausea and vomiting, drowsiness, ataxia, dizziness, headache, tremor, hyperkinesia, emotional lability, irritability, insomnia, anxiety, anorexia and diplopia. Irritability and behavioural change can be severe. Rare side effects include confusion, psychosis, leucopenia, thrombocytopenia and alopecia. Levetiracetam should be started at a low dose and titrated up weekly to initial target dosage. However, if there are clinical needs and under supervision, levetiracetam can be started at the maintenance dose either orally or as an intravenous infusion. No clinically relevant interaction with other drugs has yet been described; however, it is likely that it has pharmacodynamic interactions with other antiepileptic drugs.

Phenobarbital

Phenobarbital, the oldest barbiturate, is an effective broad-spectrum antiepileptic against most seizure types, intravenously or chronic oral use. Currently, it is hardly used in developed countries as a chronic oral use drug, although it is used in emergency situations intravenously. In patients controlled at low daily doses, phenobarbital is a relatively cost-effective and relatively well-tolerated medication and is used especially in resource-poor countries. The main disadvantages of phenobarbital are its potential to affect cognition or pharmacokinetics interactions. Common side effects are drowsiness, depression, lethargy, cognitive slowing, Dupuytren contracture, ataxia and allergic skin reactions. In the elderly, hyperactivity, restlessness and confusion may be seen, while hyperkinesia is a problem in children. Megaloblastic anaemia is a chronic side effect and the use of concomitant folic acid supplementation is recommended. Phenobarbital interacts with a number of drugs, antiepileptic or otherwise, and this must be taken into account when using it. It interacts with steroids, antibiotics, oral contraceptives, tricyclic antidepressants, antipsychotic drugs, antineoplastic and other drugs. It decreases the levels of carbamazepine, lamotrigine, phenytoin, valproate, zonisamide and ethosuximide.

Phenytoin

Phenytoin, a hydantoin, is an effective oral treatment of partial seizures and tonic–clonic seizures and is also useful intravenously in status epilepticus. However, because of its great potential to cause chronic side effects and pharmacokinetic interactions, it is now not used as first line therapy in many countries. The most common side effects include cosmetic changes as gingival hyperplasia, acne, hirsutism, facial coarsening and neuropsychiatric disturbance, particularly depression, fatigue and cognitive slowing. Other side effects include nausea, tremor, paraesthesias, dizziness, headache, anorexia and skin rash. Rarely, it may cause hepatotoxicity, peripheral neuropathy, Dupuytren contracture, lymphadenopathy, osteomalacia, megaloblastic anaemia, leucopenia, thrombocytopenia, lupus erythematosus and Stevens–Johnson syndrome. The use of concomitant folic acid supplementation with phenytoin is recommended. It has non-linear pharmacokinetics and this can result in large increases in plasma concentrations even with small dose increments; conversely, levels may fall abruptly even with modest dose reduction. Routine monitoring of plasma levels of phenytoin is recommended. Phenytoin is a potent enzyme inducer, and as such can be expected to lower levels of other drugs such as carbamazepine, phenobarbital, and other antiepileptic drugs, anticoagulants, amiodorone, antihypertensive drugs (including losartan), chloramphenicol, digoxin, statins, steroids, ciclosporin, sulphonamides, imidazole antifungal drugs, tricyclic antidepressants, antipsychotic drugs, antineoplastic drugs, and the oral contraceptives. Conversely, the metabolism of phenytoin can be inhibited by enzyme inducers such as allopurinol, chloramphenicol, cimetidine, isoniazid, metronidazol, phenothiazine and sulphonamides.

Pregabalin

Pregabalin, a gabapentin analogue, is a second line antiepileptic for partial seizures. It has no indication in any other seizure type. In addition to epilepsy, pregabalin also has use in generalized anxiety disorder and neuropathic pain. Its side effects include dizziness, drowsiness, irritability, speech disorder, paraesthesia, confusion, fatigue, weight gain and visual disturbances. Less common side effects include increased salivation, taste disturbance, oedema, nasal dryness, stupor, depression, insomnia, mood swings, asthenia, muscle cramp and rash. Rare effects include pancreatitis, arrhythmia, rhinitis, menstrual disturbances, breast discharge, breast hypertrophy, neutropenia, rhabdomyolysis and renal failure. Like gabapentin, it seems devoid of any clinically significant interactions.

Primidone

Primidone is a barbiturate that is largely metabolized to phenobarbital, and its effects are very similar to those of phenobarbital. It is currently rarely used for the treatment of epilepsy.

Oxcarbazepine

Oxcarbazepine is a structural variant of carbamazepine with a similar efficacy as an add-on drug for refractory partial seizures and as a first line agent in previously untreated patients with tonic–clonic and partial seizures. It also shares many side effects with carbamazepine but overall oxcarbazepine is perceived as being better tolerated. Common side effects include nausea, dizziness, headache, drowsiness, agitation, lethargy, ataxia, impaired concentration, depression, tremor, hyponatraemia; acne, alopecia, skin rash and diplopia. Rare side effects include hepatitis, pancreatitis, arrhythmias, hypersensitivity reactions, thrombocytopenia, systemic lupus erythematosus and Stevens–Johnson syndrome. Hyponatremia is more marked than with carbamazepine and occasionally leads to confusion and increase of seizures. Cross-sensitivity with carbamazepine in skin rashes is seen about one-third of patients. Oxcarbazepine should be started at a low dose and titrated up weekly to initial target dosage. However, if there are clinical needs and under supervision, oxcarbazepine can be started at the maintenance dosage. It has less potential for pharmacokinetic interactions than carbamazepine but nevertheless interactions occur, e.g. with oral contraceptives, and comedication with oxcarbazepine can significantly lower lamotrigine levels. Oxcarbazepine can lower the levels of ciclosporin.

Tiagabine

Tiagabine, a GABAergic drug, has a mild to moderate efficacy in the control of partial seizures. It has no indication in other seizure types and indeed is known to exacerbate generalized seizures. The most common adverse events are CNS-related and consist of sedation, tremor, headache, mental slowing, emotional lability, speech impairment, tiredness, depression and dizziness. Rarely, confusion, psychosis and leucopenia may occur. Increases in seizure frequency and episodes of non-convulsive status may also occur, particularly when used in idiopathic generalized epilepsy. Enzyme inducers tend to accelerate the clearance of tiagabine and higher doses may be required if they are used concomitantly.

Topiramate

Topiramate, a sulfamate-substituted monosaccharide, is a broad-spectrum drug for partial and secondarily generalized seizures. Topiramate can cause predominantly neurological side effects, particularly at high dosage and if titrated too fast. These adverse effects include headache, sedation, impaired memory and concentration, speech disturbance, asthenia, anxiety, depression, sleep disorders, visual disturbances and confusion. Nausea, abdominal pain, dry mouth, taste disturbance, anorexia, weight loss and paraesthesia can also occur. Very rarely, it may cause acute myopia with secondary angle-closure glaucoma which is reversible. To lessen the incidence of treatment limiting side effects, topiramate needs to be started at a low dosage and it should be titrated up slowly. Topiramate is a weak inhibitor of carbonic anhydrase and as such is associated with an increased risk of renal stones; patients should be advised to increase fluid intake during treatment to decrease this risk. Enzyme inducers tend to accelerate the clearance of topiramate and higher doses may be required if they are used concomitantly.

Valproate

Valproate, a pentanoic acid, is a first line drug for initial treatment of idiopathic generalized epilepsy with absences and juvenile myoclonic epilepsy and for generalized tonic clonic seizures on awakening. It is a broad-spectrum antiepileptic drug and is also efficacious against partial seizures. Common side effects include tremor, behavioural disturbances, weight gain, thrombocytopenia, menstrual disturbances, ankle swelling and usually minor loss of hair. Cognitive impairment is sometimes seen. Encephalopathy has been occasionally reported, possibly because of hyperammonemia, which is a common result of valproate therapy. Rare cases of fatal hepatotoxicity have occurred, especially in infants during polytherapy. The use of valproate during pregnancy is associated with an increased risk of teratogenicity and there are concerns that it could also lead to increased educational needs in children exposed to it *in utero* even when there is no malformation. Valproate should therefore be used cautiously in women with childbearing potential. Valproate mildly inhibits the metabolism of other antiepileptic drugs which is rarely of clinical relevance except when prescribed with lamotrigine. Valproate inhibits the metabolism of lamotrigine, leading to greatly elevated plasma levels. Interactions with phenytoin and carbamazepine can be significant also. Carbapenem antibiotics cause a profound lowering of valproate levels and this combination should be avoided. Valproate concentrations are also lowered by some antineoplastic drugs. Valproate concentrations can be greatly elevated with co-medication with antidepressant drugs. The full pharmacological action of valproate may take several weeks to develop after steady-state concentrations have been reached. Valproate monitoring is not recommended as there is no relationship between clinical effects and the plasma concentration.

Vigabatrin

Vigabatrin, a GABAergic drug, is a last resort drug in refractory partial seizures (it is still a first line drug for infantile spasms). Its use is currently limited by the occurrence of visual field defects in at least one-third of patients on long-term therapy. Irreversible visual field defects, which may be asymptomatic in the early stages, can lead to blindness.

Zonisamide

Zonisamide, a sulphonamide, is a broad-spectrum drug effective for partial seizures and for refractory generalized seizures particularly myoclonic. The common side effects of zonisamide include nausea, drowsiness, dizziness, irritability, depression, ataxia, speech disorder, impaired memory and attention, anorexia and weight loss, pyrexia, diplopia and skin rash. Less common effects include psychosis and hypokalaemia. Rare side effects include hallucinations, suicidal ideation, amnesia, coma, neuroleptic malignant syndrome, heat stroke, hydronephrosis, renal impairment, blood disorders, rhabdomyolysis, impaired sweating, Stevens–Johnson syndrome, hepatitis and pancreatitis. Zonisamide is associated with an increased risk of kidney stones; patients should be advised to increase fluid intake during treatment to decrease this risk. Enzyme inducers tend to accelerate the clearance of zonisamide and higher doses may be required if they are used concomitantly.

Emergency drug treatment

Prolonged convulsions or serial seizures

If a tonic–clonic seizure continues for 5–10 minutes, benzodiazepine therapy, either intravenously or rectally, is usually given. Undiluted IV diazepam is given at a rate not exceeding 2–5 mg/min, using the Diazemuls© formulation. The adult bolus intravenous or rectal dose is 10–20 mg, and in children the equivalent bolus dose is 0.2–0.3 mg/kg. Intravenous lorazepam is an alternative with some advantages over IV diazepam (longer time of action, less risk of cardiovascular collapse) The dose is 4 mg in adults or 0.1 mg/kg in children. Out of hospital, buccal midazolam 10 mg is increasingly used as an alternative to rectal diazepam and is preferred by patients and carers for ease of use and preservation of dignity.

If clusters of seizures occur, acute therapy after the first seizure can be given to prevent subsequent attacks. Oral clobazam (10–20 mg) is a common choice, and will take effect within 1–2 hours and last for 12–24 hours.

Tonic–clonic status epilepticus

If tonic–clonic status epilepticus is allowed to persist for more than about 2 hours, there is a substantial risk of seizure-induced cerebral damage. The risk rises the longer the seizures continue. For this reason, the drug treatment of tonic–clonic status epilepticus is best divided into stages:

1 First stage (early status) is defined as the first 30 minutes of seizure activity;

2 Second stage (established status) is reached if early stage treatment fails;

3 Third stage (refractory status) is reached if seizures continue for more than 1–2 hours after initiating therapy, despite early or established stage therapy.

A systematic protocol-driven approach is important in this emergency situation. The choice of drug regimen is somewhat arbitrary. A protocol favoured is shown in Table 6.23 and details of the drugs used are given in Tables 6.24 and 6.25.

Epilepsy surgery

Epilepsy surgery can be carried out with three objectives: to stop seizures, to ameliorate the seizures or to remove a progressive lesion or one that carries other risks such as haemorrhage. Here we concentrate on the assessment, surgery and outcome of those who have surgery primarily for their epilepsy. These are patients whose epilepsy proves resistant to antiepileptic drugs. Given the conservative estimates that approximately 20% of patients are resistant to treatment with antiepileptic drugs, and 50/100,000 people per year develop epilepsy, then every year approximately 1/10,000 people develop refractory epilepsy (i.e. 6000 every year in the UK). In the UK, approximately 1000 of these patients (3% of the incident cohort) are suitable for

Table 6.23 Protocol for the treatment of status epilepticus in adults.

Stage of early status (0–30 min)
Lorazepam 4 mg IV bolus (can be repeated once)

↓ (if seizures continue after 30 min)

Stage of established status (30–60/90 min)
Phenobarbital IV infusion 10 mg/kg at 100 mg/min
or
Phenytoin IV infusion 15 mg/kg at 50 mg/min
or
Fosphenytoin IV infusion 15 mg PE/kg at 100 mg PE/min
or
Valproate IV infusion 25 mg/kg at 3–6 mg/kg/min

↓ (if seizures continue after 30–90 min)

Stage of refractory status (>60/90 min – general anaesthesia)
Propofol: IV bolus 2 mg/kg, repeated if necessary, and then followed by a continuous infusion of 5–10 mg/kg/hour initially, reducing to a dose sufficient to maintain a burst suppression pattern on the EEG (usually 1–3 mg/kg/hour)
or
Thiopental: IV bolus 100–250 mg given over 20 seconds with further 50 mg boluses every 2–3 min until seizures are controlled, followed by a continuous iv infusion at a dose sufficient to maintain a burst suppression pattern on the EEG (usually 3–5 mg/kg/hour)
or
Midazolam: IV bolus 0.1–0.3 mg/kg at a rate not exceeding 4 mg/min initially, followed by a continuous IV infusion at a dose sufficient to maintain a burst suppression pattern on the EEG (usually 0.05–0.4 mg/kg/hour)

When seizures have been controlled for 12 hours, the drug dosage should be slowly reduced over a further 12 hours. If seizures recur, the general anaesthesic agent should be given again for another 12 hours, and then withdrawal attempted again. This cycle may need to be repeated until seizure control is achieved

Table 6.24 Drugs used in the pre-anaesthetic management of convulsive status epilepticus.

	Route of administration	Adult dose	Paediatric dose
Diazepam	IV bolus (not exceeding 2–5 mg/min)	10–20 mg	0.25–0.5 mg/kg
	Rectal administration	10–30 mg	0.5–0.75 mg/kg*
Midazolam	IM or bucal	5–10 mg*	0.15–0.3 mg/kg*
	IV bolus	0.1–0.3 mg/kg at 4 mg/min*	
	IV infusion	0.05–0.4 mg/kg/h	
Clonazepam	IV bolus (not exceeding 2 mg/min)	1–2 mg at 2 mg/min*	250–500 mg
Fosphenytoin	IV bolus (not exceeding 100 mgPE/min)	15–20 mg PE/kg	
Lorazepam	IV bolus	0.07 mg/kg (usually 4 mg)*	0.1 mg/kg
Phenytoin	IV bolus/infusion (not exceeding 50 mg/min)	15–20 mg/kg	20 mg/kg at 25 mg/min
Phenobarbital	IV bolus (not exceeding 100 mg/min)	10–20 mg/kg	15–20 mg/kg
Valproate	IV bolus	15–30 mg/kg	20–40 mg/kg

* May be repeated. PE, phenytoin equivalents.

Table 6.25 Anaesthetic drugs used in status epilepticus.

Midazolam	0.1–0.3 mg/kg at 4 mg/min bolus followed by infusion of 0.05–0.4 mg/kg/hour
Thiopentone	100–250 mg bolus over 20 seconds then further 50-mg boluses every 2–3 min until seizures are controlled. Then an infusion of 3–5 mg/kg/hour to maintain burst suppression
Pentobarbital	10–20 mg/kg bolus at 25 mg/min followed by an infusion of 0.5–1 mg/kg/hour increasing to 1–3 mg/kg/hour to maintain burst suppression
Propofol	2 mg/kg bolus followed by an infusion of 5–10 mg/kg/hour to maintain burst suppression

presurgical assessment of whom approximately half (500) patients per year are suitable for surgery. As surgical techniques and presurgical evaluation improve, it is hoped we will be able to identify a greater number of patients who may benefit from epilepsy surgery. In addition to those undergoing presurgical evaluation, there are also a growing number of palliative operations, in particular vagal nerve stimulation.

All patients who are being considered for surgery need a detailed presurgical evaluation, this is necessary not only to assess the likelihood of surgical success, but also to establish the suitability of the patient, to determine the type of operation (including further invasive investigations) and to assess the potential risks.

Who is suitable for presurgical assessment?

The main criterion for selecting patients for presurgical assessment is drug resistance. There therefore has to have been an adequate trial of medical therapy, but what is adequate? This question has generated a certain amount of debate. Although some studies have suggested that failure to respond (rather than withdrawal because of side effects) to an initial treatment results in 11% chance of becoming seizure free with subsequent treatments, this is probably overly pessimistic. Patients who are turned down for surgery or refuse surgery have a 15–25% chance of becoming seizure free over subsequent years. This is partly because patients seen at time of presurgical assessment are at the nadir of their disease, but also new antiepileptic drugs have had an impact; adding new antiepileptic drugs in a sequential fashion to the drug regimen of refractory patients can render one-quarter of these patients seizure free. A generally accepted minimum is that a person should have tried at least two first line antiepileptic drug treatments at appropriate dosage over a period of 2 years. Whether to continue with trials of antiepileptic drugs or to refer directly for surgery depends upon the chance of surgical success and the severity of the epilepsy.

Epilepsy severity is difficult to characterize and to evaluate; it has to be considered on an individual basis and assessed in the light of the likely success and adverse effects of surgery. It is also important to consider the morbidity and mortality attached to even infrequent seizures. SUDEP has a particularly high incidence in patients evaluated for but refused surgery – over 1% per year. Nevertheless, it has to be established that reducing the frequency or stopping the seizures will result in a significant improvement of quality of life. In people with multiple problems (e.g. epilepsy and severe psychiatric disease or severe learning difficulties), the epilepsy may only contribute a small amount to the person’s disability. Indeed, during the presurgical period it is paramount to ascertain the expectations that both carers, family and the patient have of surgery. Only too often, people feel that epilepsy surgery will resolve all problems, and so are disappointed if seizure freedom has had little impact on their lives. Counselling is therefore necessary so that all involved can have realistic expectations.

A further consideration is the risk of operation. Thus, even in cases where there may be a high chance of seizure freedom, the risks of surgery may be unacceptable. This is dependent not only upon the specific operation (e.g. removal of eloquent cortex or memory problem following dominant temporal lobe resection), but also upon the health of the individual (e.g. surgery in patients with other medical conditions may represent an unacceptable risk). However, the immediate risks of operation may be offset by longer term benefits (e.g. the mortality of the operation may be offset by the reduction in the chance of SUDEP, or the loss of memory following an operation may be offset by the risks to memory of continued seizures).

Pre-operative evaluation

Pre-operative evaluation is a multidisciplinary process, and involves not only determining the nature of the operation, but also the risks and possible benefits. This requires assessment and discussion involving the neurologist, neurosurgeon, psychologist, psychiatrist, neurophysiologist and radiologist.

There are two main strategies for the surgical treatment of seizures. The first involves curative resective surgery, in which the aim of the surgery is the removal of the epileptogenic zone (defined as the area that has to be removed in order to render someone seizure free). This can be restricted to a focal lesion or may involve lobar or multi-lobar resection (e.g. hemispherectomy). The second approach is palliative in order to decrease the frequency or severity of seizures.

The assessment of curative resective surgery is mainly aimed at identifying the epileptogenic zone. This relies upon the convergence of presurgical investigations including clinical history, seizure semiology, scalp EEG, neuroimaging and neuropsychometry. Discordance between these may lead to a lesser chance of surgical success and the need for further investigation (imaging, invasive EEG recordings). The relative weight that is lent to each of these investigations varies depending on the type of operation and the pathogenesis of the epilepsy and in many instances is either controversial or undetermined.

Clinical history

The clinical history contains a number of details that are critical in pre-operative assessment. The age of the patient is relevant as surgery has a greater neuropsychological impact on older patients. Further, there is some evidence to suggest that the longer someone has had mesial temporal lobe epilepsy, the less chance that there will be of long-term seizure freedom following resection. Handedness gives an indication of hemisphere dominance. Antecedent history is of relevance, for example a history of febrile seizures is a good prognostic factor for surgery in those with hippocampal sclerosis, but a poor prognostic factor in those undergoing frontal lobe resection. The semiology of the seizures is critical (see below). The presence of secondary generalized seizures is predictive of poorer outcome. It is also important to have details of social support and psychiatric concerns (see below).

Psychiatric history

A psychiatric assessment is necessary prior to surgery. First, there are relative contraindications to surgery including active depression or psychosis that will need treating. It is also important to ascertain whether the person would be able to sign an informed consent. The additional presence of dissociative seizures (non-epileptic attacks with a psychological basis) is a relative contraindication, as they can often worsen after resective surgery. The risks of post-resective depression and/or psychosis also need to be estimated. Certain patients may require additional psychiatric support both peri- and post-operatively. About one-quarter of patients have transient mood disturbances in the first year following surgery and approximately 10% may require treatment for depression.

Neuroimaging

High-quality MRI has become a cornerstone of pre-operative assessment. The presence of an identifiable well-defined lesion has a considerable impact on the surgical approach and the prognosis for surgery. If it can be shown that a lesion is the substrate for the epilepsy, then complete resection of that lesion stands a high chance of rendering the patient seizure free, while failure to resect or incomplete resection carry a poorer prognosis. The presence of an identifiable lesion on MRI also increases the chance of surgical success compared to 'MRI-negative' patients. At a minimum the MRI investigation should involve T2-weighted sequences, proton density sequences, FLAIR sequences and T1-weighted volume acquisition (partition size less than 1.5 mm). Finer cuts and also other sequences may also be helpful.

The role of FDG-PET, other PET ligands and ictal SPECT remains less certain, but they are useful in MRI-negative patients, on occasions when there is discordance between other investigations and in patients in whom there are extensive or multiple pathologies (e.g. tuberous sclerosis).

Functional MRI can be used to identify eloquent cortex and to lateralize language. It is likely that as a non-invasive investigation, fMRI will be increasingly used as a method for correlating structure with function such as in the assessment of memory.

Neurophysiological investigation

Scalp EEG with video has become a necessary investigation in pre-operative assessment, although there are cases with clear-cut pathology, typical history and typical interictal EEG in whom video-EEG telemetry may be unnecessary.

The interictal EEG is useful and can be of prognostic relevance (e.g. atypical epileptiform abnormalities in patients with hippocampal sclerosis predicts poorer outcome). However, ictal video-EEG telemetry in order to define the electroclinical origin of the seizure is usually required. The hope is that this is concordant with neuroimaging, as discordance reduces the chance of a good outcome and can necessitate invasive EEG recordings. How many seizures need to be recorded varies depending on aetiology and results of neuroimaging. If there are doubts about laterality or localization then more seizures will need to be recorded. Protocols for electrode placement and drug reduction vary from unit to unit. In all patients being investigated for temporal lobe epilepsy additional EEG electrodes covering the sphenoidal area are used (the authors use surface zygomatic electrodes and have found no significant advantage in using needle sphenoidal electrodes).

Intracranial EEG monitoring over 1–2 weeks with subdural electrodes and/or depth electrodes may be required in cases of discordance to test a hypothesis, e.g. if video-EEG telemetry is discordant with an MRI demonstrating only hippocampal sclerosis. Invasive recordings are also necessary with certain pathologies such as cortical dysplasia or encephalomalacia in order to define accurately the epileptogenic zone. Acute electrocorticography at the time of resection is used in some units to define the extent of resection, but we usually use more chronic recordings. Depth electrodes can only cover a small area (usually there are 6–8 contacts) and have approximately a 1% risk of haemorrhage or infection. Subdural grids do not broach the pial boundary, have a lesser chance of causing haemorrhage and can cover a much larger area. The disadvantage of subdural grid electrodes is that they require a craniotomy and carry a higher risk of infection (approximately 3–5%); over one-quarter of patients develop an aseptic meningitis – usually restricting recordings to 10 days or less. The placement of the electrodes is dependent on the hypothesis that is to be tested. Intracranial stimulation either during awake craniotomy or with chronic subdural electrodes may also be necessary to delineate eloquent cortex and so determine the safe margins of resection.

The role of magneto-encephalography (MEG) has yet to be defined. Measuring changes in the electric field has the advantage of detecting currents that run perpendicular to the brain surface (such currents are often undetectable by scalp EEG). MEG may also detect spikes that originate deeper in the cortex. The limitation is that MEG cannot be used continuously to detect ictal changes.

Neuropsychology

Neuropsychological assessment has a role in localization; neuropsychological deficits implicating cortex distinct from the putative epileptogenic cortex may indicate more widespread cortical pathology. Psychometric testing may also be used to estimate the psychological sequelae of epilepsy surgery. Most commonly, this is in the context of memory deterioration following temporal lobe resection.

Injection of sodium amytal into each hemisphere (the 'amytal test') to anesthetize each hemisphere in turn was originally devised to lateralize language in uncertain cases, but this is now increasingly determined by fMRI. However, the amytal test was extensively used to determine the possible neuropsychological sequalae of temporal lobe resection. The problems are that, because of variations of blood flow, access of the drug to relevant structures (e.g. the mesial temporal structures) and cross flow, the amytal test can be misleading. More selective amytal tests can be performed by super-selective injections of amytal into specific cerebral vessels; however, these are more technically challenging and provide a greater risk for the patient. In some units, an intracarotid sodium amytal test is used in every patient undergoing temporal lobe resection. Other units restrict the use of this test to patients in whom there is discordance between neuropsychometric testing and neuroimaging. The authors now rarely use the amytal test and depend upon the information gleaned from standard neuropsychometric testing and neuroimaging. The amytal test has a 0.5% morbidity.

Counselling

All patients should be counselled prior to surgery. They should be given details of risks and benefits; the authors find it advantageous not only to record these discussions in the notes, but also to send a letter to the patient with all these details. An estimate of the odds of success along with associated risks including catastrophic risks (stroke/death), neuropsychological risks, neuropsychiatric risks and more specific risks (e.g. visual defect) is given to the patient. The counsellor will also describe in more detail the practicalities (e.g. the length of time off work). They will also ascertain the degree of postoperative social support.

Surgery

Surgery for epilepsy can be divided into resective, curative surgery and palliative surgery, although there is sometimes a blur between these, as some forms of palliative surgery can render patients seizure free, and on some occasions resective surgery is performed to palliate rather than necessarily cure the epilepsy.

Curative resective surgery

Although resective surgery has been the mainstay of curative surgical techniques, other approaches such as stereotactic radiosugery using a gamma knife have grown in popularity. The gamma knife is ideal for lesions that are difficult to resect (e.g. hypothalamic hamartomas) or for patients who are unlikely to be able to tolerate resective surgery. Whether the technique has a place in other situations remains to be determined. The main disadvantages are a lack of long-term follow-up and a significant delay from the radiosurgery to obtaining maximum benefit (as long as 1 year).

Lesionectomy

Patients with discrete lesions have a good outcome from resective surgery, provided that the lesion can be completely removed and that there is no concomitant pathology. Thus, patients with dysembryoplastic neuro-epithelial tumours or discrete vascular lesions have a 50–80% chance of seizure freedom following removal of the lesion. In situations where the lesion is less well defined or is associated with more widespread abnormalities, the chance of seizure freedom drops markedly. Thus, focal cortical dysplasia visualized on MRI may only be the 'tip of the iceberg' and resection margins invariably have to be delineated using intracranial recordings. Nevertheless, resections of focal cortical dysplasia have a 40–50% chance of rendering someone seizure free. Temporal lobe lesion are frequently associated with hippocampal sclerosis, and experience dictate that removal of both the lesion and the hippocampus is usually necessary for a successful outcome. The complications of surgery depend upon the location of the lesion, and in particular its proximity to eloquent cortex.

Temporal lobe epilepsy

Temporal lobe resection is the most common operation for seizure control. The most common pathology is hippocampal sclerosis. There have been a variety of surgical approaches to temporal lobe resection. These approaches minimize the temporal neocortex resection, while maintaining the hippocampal resection, and fall broadly into two camps: anterior temporal lobectomy or selective amygdalo-hippocampectomy. The advantages and disadvantages of each of these approaches are probably a minor consideration compared to the effects of surgical experience. These operations result in approximately 50–70% of patients becoming seizure free (this figure may be higher in those with hippocampal sclerosis and concordant investigations) and 20% are improved. However, the chances of remaining seizure free diminish over time (probably by 3% per year for the first 5 years). The overall mortality of temporal lobectomy is less than 0.5%. A transient hemiparesis can occur in up to 5%, but the risk of permanent hemiparesis is less than 1%. The chance of significant memory decline depends upon baseline memory test, age and side of operation (dominant versus non-dominant). Significant visual field defects occur in 10%, and 5% of patients in the UK may be unable to drive because of these. Postoperative depression is not uncommon. Postoperative psychosis is less common and usually occurs in patients whose seizures are continuing.

Extratemporal surgery

Extratemporal surgery is performed less frequently and mainly consists of frontal lobe surgery. The presence of a lesion is the most important predictor of surgical success. Overall, approximately 40–50% become seizure free, but a normal MRI reduces these odds. The risks of operation are related to the site of resection.

Hemispherectomy

This is particularly effective in controlling seizures, with approximately 80% becoming seizure free. This operation is only suitable for people with a profound hemiparesis, and care needs to be taken if it is the dominant hemisphere. Early theories concerning language development suggested that resection of the dominant hemisphere should not occur after the age of 6 years, but recent experience suggests a cut-off of 9 years and indeed language recovery has been noted at even later ages. The operation is usually carried out in people with extensive abnormalities of one hemisphere or with a pathology affecting one hemisphere (e.g. Rasmussen's encephalitis). Mortality is approximately 1–2%. In the past, long-term outcome was poor because of problems resulting from hydrocephalus and superficial haemosiderosis.

These risks have diminished with modern refinements of the operation – most centres now carry out a functional hemispherectomy. In this operation, the temporal lobe is removed, a corpus callosotomy is performed and the frontal and occipital lobes are disconnected.

Palliative procedures

These operations aim to reduce the frequency or severity of seizures but rarely render people seizure free.

Corpus callosotomy

Callosotomy is considered when resective surgery is not possible and when atonic, tonic or, more controversially, tonic–clonic seizures are a prominent and disabling part of the patient's epilepsy. The chances of seizure freedom with this operation are slim, 5%, and the morbidity from this operation can be considerable. When language representation occurs in both hemispheres, then language problems can occur (some centres advocate an amytal test in all patients). Furthermore, disconnection syndromes with apraxia and 'alien' hand are the cause of considerable disability. These tend to be more prevalent in older patients (after the age of 12 years). Because of this risk, the operation is often performed as a two-stage procedure with first section of the anterior two-thirds and then, if seizure control is inadequate, a further procedure to section the posterior one-third can be considered. Because of the morbidity and disappointing long-term results, many centres would use vagal nerve stimulation in preference (see below).

Multiple subpial transection

This procedure is considered when eloquent areas of cortex form part of the epileptogenic zone. It is nowadays usually performed as an adjunct to, and in combination with, a cortical resection. The concept around which this procedure is based is that the functional cortical activity occurs in a radial plane, while seizures spread in a tangential plane. Thus, by making radial sections it should be possible to prevent seizure spread without interfering with physiological function. The cortex is exposed and acute corticography is used to determine the extent of the irritative zone. Radial cuts are made at intervals of less than 5 mm and the procedure is deemed successful once interictal discharges are abolished or minimized. The success rate for this procedure is contentious, with some groups reporting 60–70% having a 95% reduction in seizure frequency. However, 20–30% of patients will have a resultant deficit, and there is a significant long-term relapse rate. The operation is now largely confined to treating patients with Landau–Kleffner syndrome or occasionally carried out in conjunction with a cortical lesion resection.

Stimulation

The use of stimulation of various structures has a long and chequered history, but has recently been placed on a more scientific basis with better trials and a better understanding of mechanisms of action.

Vagal nerve stimulation for epilepsy has now been licensed throughout the world. This involves the placement of a stimulator under the skin with a wire to the left vagus nerve which is then intermittently stimulated. The stimulation parameters vary but are usually in the range: amplitude 0.25–3.5 mA; pulse width 250–500 µs; frequency 20–30 Hz; duty cycle 30 seconds on, 5 minutes off. In addition, patients can activate a cycle with a magnet in order to try to abort a seizure during an aura. The success rate is poor. Approximately 50% of patients can expect a 50% or greater reduction in seizures. Good results have been reported in patients with tonic or atonic seizures, and vagal nerve stimulation is increasingly being used by some centres in preference to corpus callosotomy. Dyspnoea, throat pain and hoarse voice are the main adverse events.

Stimulation of other targets such as the thalamus, subthalamic nuclei and the hippocampus are still in the early stages of development, but these methods are beginning to show promise not only as palliation, but also as potential cures.

Follow-up

All patients undergoing epilepsy surgery need close follow-up in order to detect postoperative problems (e.g. depression, seizure recurrence), to inform surgical practice and to counsel patients regarding such issues as drug withdrawal. The authors routinely repeat neuropsychological tests and MRI at 3–6 months following surgery, and then may repeat the neuropsychology again at a year.

If a patient becomes seizure free, then drug withdrawal will need to be considered. In the authors' series less than 30% of those who are seizure free following surgery choose to withdraw AEDs completely. In those who do wish to reduce or withdraw medication, some authorities start withdrawal at 1 year postoperatively and slowly taper over the subsequent year (drug withdrawal thereby usually occurs by 2 years post-operation). Others withdraw drugs more slowly, and the authors' practice is not to withdraw drugs in the first five years. The occurrence of early seizures, the inability to remove all the pathology, normal preoperative MRI, longer duration of epilepsy and older age all predict a less successful withdrawal from drugs.

Other aspects of treatment

Role of epilepsy specialist centres

In the UK, it is an accepted recommendation that all patients with suspected epilepsy should be referred to the specialist neurology services for diagnosis, and that patients with chronic epilepsy should be referred to an epilepsy specialist.

Epilepsy clinic

An epilepsy clinic is defined as a clinic run by a specialist with an interest in epilepsy (usually a neurologist but could be a GP or psychiatrist) in which all the clientele have epilepsy. About 30% of patients who develop epilepsy will continue to have seizures despite treatment with antiepileptic drugs, and most of these will require further specialist follow-up. The NICE guidelines propose that the diagnosis of epilepsy should be established by specialist practitioners with training and expertise in epilepsy. Treatment (where appropriate) should be initiated by the epilepsy specialist, who should also plan the continuation of treatment, and manage, or provide guidance for, withdrawal of antiepileptic drugs. A management plan should be formulated jointly by the hospital and general practice to alleviate the mismatch that could occur when the patient's epilepsy is being looked after by secondary or tertiary care, but when the patient has access only to the GP when acute problems occur.

Epilepsy centre

An epilepsy centre is directed by a neurologist (or occasionally another physician) with a special interest in epilepsy, but emphasis is on shared care between general practice and hospital. Epilepsy centres have a multidisciplinary team to deal with patients who have previously proved refractory to treatment. The function of this service is to:

- Confirm the diagnosis;
- Initiate treatment, if indicated;
- Provide initial counselling and information to patients and their families;
- Monitor the response to the initial treatment; and
- Refer the patient back to the GP if the condition is stable.

There are several epilepsy centres in the UK specializing in the assessment and care of children (i.e. National Centre for Young People with Epilepsy [NCYPE], David Lewis Centre), or adults (i.e. National Society for Epilepsy [NSE], David Lewis Centre) with complex epilepsy and other neurological conditions, including learning disability and challenging behaviour. These epilepsy centres provide a range of medical, educational, residential and assessment services tailored to the needs of each individual. Patients benefit from the expert care of multidisciplinary teams consisting of neurologists, epilepsy specialist nurses, neurological or learning disability psychiatrists, neuropsychologists, physiotherapists, occupational therapists, social worker, teachers and others. An epilepsy centre offers specialized and appropriate investigations, including:

- Routine and ambulatory EEG recordings as well as video-EEG telemetry;
- Therapeutic drug monitoring; and
- Access to specialized and dedicated neuro-imaging (MRI) facilities.

However, these tests should not be used routinely, but only when clinically indicated. Epilepsy clinics and centres are considered to be better than general neurology clinics in the management of people with epilepsy: they are more likely to follow-up patients and to provide a greater continuity of care, perform fewer CT scans, but more antiepileptic drug concentration testing and EEGs. Patients attending these clinics are either given or retain more information, and are generally more satisfied with the service provided compared with those attending general neurology clinics. Although the epilepsy clinics and centres are more expensive, the additional costs can be offset by a reduction in other services, such as the number of GP visits, the amount of antiepileptic drugs prescribed, unnecessary CT scans and hospital admissions for either drug toxicity or poor seizure control.

Driving

In the UK, it is the role of the Driving and Vehicle Licensing Agency (DVLA) to issue driving licenses. Epilepsy is a condition in which special rules for licensing apply, and the patient must notify the DVLA of the occurrence of epilepsy. In other countries different rules apply.

Licensing rules in the UK

Group 1 licensing

Driving rules for a group 1 licence (a normal driving licence for car and motorcycles) are:

1 A person who has had an epileptic attack while awake must refrain from driving for 1 year from the date of the attack before a driving licence may be issued.

2 A person who has had an attack while asleep must also refrain from driving for 1 year from the date of the attack. However, if a pattern of sleep-only attacks has been established for 3 years or more, without any awake attacks occurring during this period, licensing is allowed even if sleep attacks have occurred in the preceding year; and (in both cases)

3 The person must comply with advised treatment and check-ups for epilepsy, and the driving of a vehicle by such a person should not be likely to cause danger to the public.

Group 2 licensing

Group 2 licences cover the driving of lorries, buses and taxis, and the rules are much stricter. During the period of 10 years immediately preceding the date when the licence is granted the applicant/licence holder should be:

1 Free from *any* epileptic attack; and

2 Have not required medication to treat epilepsy; and

3 Should not otherwise be a source of danger while driving.

For both types of licence

A person having a solitary seizure must normally satisfy the above regulations, except where a solitary seizure occurs in relation to alcohol and/or drug or substance misuse.

A person with a structural intracranial lesion who has an increased risk of seizures will not be able to drive vehicles of this group until the risk of a seizure has fallen to no greater than 2% per annum, the level recommended by the panel, which permits compliance with the regulations.

A provoked or acute symptomatic seizure may be dealt with on an individual basis by the DVLA if there is no previous seizure history. The decision to prohibit driving in this situation will be influenced by such aspects as:

1 Whether the provoking stimulus carries any risk of recurrence;
2 Whether the stimulus had been successfully or appropriately treated or was unlikely to occur at the wheel.

Thus, for example, the following seizures are usually considered provoked: eclamptic seizures; reflex anoxic seizures; an immediate seizure at the time of a head injury; a seizure in first week following a head injury, which is not associated with any damage on CT scanning, nor with post-traumatic amnesia of longer than 30 minutes; a seizure at the time of a stroke/TIA or within the ensuing 24 hours; or a seizure occurring during intracranial surgery or in the ensuing 24 hours. Seizures associated with alcohol or drug misuse, sleep deprivation or a structural abnormality are not considered as 'provoked' for licensing purposes.

Role of the doctor vis-à-vis the driving regulations

The following policy should be followed. The doctor must make it clear to a driving licence holder that they have a condition that may affect their safety as a driver, and therefore that the driver has a legal duty to inform the DVLA about the condition.

If the patient refuses to accept the diagnosis or the effect of the condition on their ability to drive, the doctor should advise the patient that a second opinion can be sought and appropriate arrangements should be made for this. It is important that the patient is advised not to drive until the second opinion has been obtained. If the patient continues to drive when not fit to do so, the doctor should make every reasonable effort to dissuade driving. If the patient continues to drive despite the above measures, the doctor should disclose relevant medical information immediately, in confidence, to the DVLA. Before giving information to the DVLA, the doctor should inform the patient of the decision to do so. Once the DVLA has been informed, the doctor should also write to the patient to say that a disclosure has been made.

Acknowledgement

Many of the figures and some of the text are drawn from *Handbook of Epilepsy Treatment* by Simon Shorvon. Published by Blackwell Publishing, 2005.

Useful websites with epilepsy information for patients

www.epilepsy.org Official portal of the International Bureau Against Epilepsy.
www.epilepsynse.org.uk Site of the National Society for Epilepsy, UK.
www.epilepsy.com Site of a US organisation providing support for epilepsy.
www.epilepsy.org.uk Site of Epilepsy Action, a UK-based charity providing support for epilepsy.
www.epilepsyfoundation.org Site of the Epilepsy Foundation for Epilepsy, a US based organisation providing support for epilepsy.
www.ninds.nih.gov/disorders/epilepsy/epilepsy.htm Patient information from the NINDS in the USA.

Further reading

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7

Cognitive Impairment and Dementia

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Introduction

Cognitive impairment is very common and accompanies many neurological as well as systemic diseases. The array of syndromes arising from damage to the neural circuitry underlying cognition can be as bewildering as the terminology. Cognitive impairment is a useful umbrella term which encompasses the severe dementia of late stage degenerative diseases such as Alzheimer's disease (AD), the mild cognitive slowing of a patient on a sedative drug and the florid confusional state or delirium in the severely systemically ill. A useful distinction, easier in theory than in practice, is the distinction between delirium and dementia. Delirium, also referred to as an acute confusional state, is characterized by fluctuation, prominent impairment of attention and/or arousal, and accompanied often by agitation and autonomic features. Delirium is commonly seen in systemic diseases and as a side effect of a variety of drugs and toxins (see delirium tremens, Chapter 18). Dementia, by contrast refers to widespread cognitive impairment in the setting of normal arousal. This distinction can be difficult especially because confusional states can supervene in patients with many forms of dementia, especially dementia with Lewy bodies (DLB), that can present with fluctuating arousal and attentional deficits.

Definitions of dementia vary. The key features of ICD and DSM definitions are that the disruption of cortical function should involve more than one cognitive domain which should include memory, more specifically episodic memory. The requirement for a memory impairment has largely been determined by the prototypic dementia Alzheimer's disease which normally has a major amnestic component. However, other dementias such as frontal lobe dementia may only develop memory impairment, late in the disease. The cognitive deficits should be sufficiently severe to cause significant social and occupational impairment. It is often assumed that dementia is progressive but a dementia can be progressive, static or reversible, depending on the aetiology. There is an increasing need to identify patients early before they fulfil the criteria of dementia, which has led to the introduction of terms such as mild cognitive impairment (MCI) to describe those patients with early disease who have not progressed to fulfil the criteria for dementia. If memory is impaired (amnestic MCI) most patients are in the early stages of AD.

A useful distinction has been drawn between patients with prominent cognitive deficits arising from pathology in the cerebral cortex (cortical dementia) and those with prominent basal ganglia, thalamic or brainstem pathology (subcortical dementia). The latter patients are often very slow but accurate and exemplified by progressive supranuclear palsy (PSP). Cortical and subcortical pathologies often overlap, but the clinical distinction is useful.

It is important to realize that:

- Dementia is a syndrome caused by many different diseases; and
- Dementia may be reversible if the correct diagnosis of the cause is made and treated.

Epidemiology: delirium and dementia

Delirium is a problem of universal importance; it is encountered in all branches of medicine, and in both community and hospital practice. It has been estimated to occur in 5–15% of patients in general hospital wards, and a higher proportion in intensive care units. A plethora of systemic and intracranial disease processes may give rise to delirium (Table 7.1); the elderly and patients with any pre-existing cognitive impairment, and those with chronic systemic illness are especially vulnerable.

Dementia is an issue of enormous medical and socio-economic significance in societies with ageing populations. Prevalence rates

Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

Table 7.1 Causes of delirium and dementia.

Category of disease	Delirium	Dementia
Acquired/sporadic		
Metabolic disturbance	Electrolyte disorders (especially hyponatraemia, hypercalcaemia), hypoglycaemia, respiratory failure/hypoxia (any cause), uraemia, liver failure, pancreatic encephalopathy, cardiac failure, dehydration, severe anaemia	Uraemia, dialysis dementia (now rare), liver failure, respiratory failure, cardiac failure, pancreatic encephalopathy, chronic/recurrent hypoglycaemia (e.g. insulinoma)
Intoxication/withdrawal syndromes	Alcohol, anticholinergics, antihistamines, anxiolytic-hypnotics, corticosteroids, anticonvulsants, cardiovascular drugs, opiates, L-dopa, dopaminergic agonists, neuroleptic malignant syndrome, prescription of multiple drugs, illicit drugs, carbon monoxide, heavy metals, herbicides (organophosphates), industrial poisons	Alcohol, carbon monoxide, heroin (inhaled), heavy metals, organic solvents, organophosphates, lithium, methotrexate, alpha-interferon
Nutritional deficiency	Thiamine (Wernicke–Korsakoff syndrome), nicotinic acid	Thiamine, vitamin B_{12}, nicotinic acid, multiple vitamin deficiencies
Endocrinopathies	Thyroid, adrenal, parathyroid, pituitary	Thyroid, adrenal, parathyroid, pituitary
Infections	Systemic Urinary tract infection, viral exanthemas, pneumonia, endocarditis, septicaemia (all causes)	
	CNS Encephalitis (especially herpes simplex), meningitis, brain abscess, HIV, cerebral malaria, neurocysticercosis, *Mycoplasma*, post-infectious syndromes	*CNS* HIV, neurosyphilis, tuberculosis, Whipple's disease, Lyme disease, cryptococcal/fungal meningitis, neurocysticercosis, JC virus (PML), measles (SSPE), encephalitis lethargica (may be post-infectious-autoimmune)
Inflammation and autoimmune	ADEM, cerebral vasculitis (primary CNS or systemic), voltage-gated potassium channel antibody/other channelopathies	Multiple sclerosis (primary progressive), cerebral vasculitis (primary CNS or systemic), neurosarcoidosis, Behçet's disease, voltage-gated potassium channel antibody/other channelopathies, anti-basal ganglia antibody syndrome, Hashimoto's encephalopathy, coeliac disease
Epilepsy	Epileptic status (non-convulsive), post-ictal states	Non-convulsive status, transient epileptic amnesia, Rasmussen's encephalitis
Neoplastic	Raised intracranial pressure (including acute hydrocephalus), carcinomatous or lymphomatous meningitis, paraneoplastic limbic encephalitis, post-radiotherapy (acute radionecrosis, thrombo-angiopathy)	Brain tumours (especially frontal/callosal/midbrain), CNS lymphoma, carcinomatous/lymphomatous meningitis, limbic encephalitis and other paraneoplastic syndromes, post-radiotherapy (accelerated cerebral atherosclerosis, radiation leucodystrophy)
Vascular	Subarachnoid haemorrhage, venous sinus thrombosis, arterial stroke (esp posterior circulation, non-dominant parietal), hyperviscosity syndromes, polycythaemia	Multiple cortical or subcortical strokes, lacunar state, strategic infarct (esp thalamus, medial frontal), hyperviscosity syndromes, polycythaemia, sickle cell disease, steal syndromes (e.g. AVM), Susac's syndrome
Head injury	Post-concussional syndrome, diffuse axonal injury, subdural haematoma, focal cerebral trauma	Subdural haematoma, repeated head injury/dementia pugilistica, late deterioration post-head injury
Other treatable causes	Pain, sleep deprivation, sensory deprivation and distortion (as in ITU), hypothermia, heat stress, postoperative recovery (multifactorial), migraine	Obstructive sleep apnoea, normal pressure hydrocephalus, obstructive hydrocephalus/aqueduct stenosis
Degenerative	Rapid cognitive fluctuation in Lewy body/Parkinson's disease dementia	Alzheimer's disease, Parkinson's disease/dementia with Lewy bodies, fronto-temporal lobar degenerations, corticobasal degeneration, progressive supranuclear palsy, motor neurone disease dementia, neurofilament inclusion body disease, Creutzfeldt–Jakob/other prion diseases
Genetic		
Metabolic	Metabolic crises in porphyria, urea cycle disorders, others	Wilson's disease, acute intermittent porphyria, lysosomal and peroxisomal storage disorders, urea cycle disorders, leucodystrophies, others
Arteriopathies	Strokes and stroke-like episodes	CADASIL, cerebral amyloid angiopathies, British dementia, Fabry's disease, others
Degenerative	Rapid cognitive fluctuation in familial parkinsonism syndromes	Familial Alzheimer's disease, fronto-temporal lobar degeneration (chromosome 17/chromosome 3/other), Huntington's disease, DRPLA, familial Parkinson's disease/Lewy body disease, mitochondrial encephalopathies, spinocerebellar ataxias, neuro-acanthocytosis, pantothenate kinase-associated neurodegeneration, neuro-ferritinopathy, neuro-serpinopathy, familial prion diseases, others (Table 7.8)

Ab, antibody; ADEM, acute demyelinating encephalomyelopathy; AVM, arteriovenous malformation; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy; DRPLA, dentato-rubro-pallido-luysian atrophy; HIV, human immunodeficiency virus; PML, progressive multifocal leucoencephalopathy; SSPE, subacute sclerosing panencephalitis.

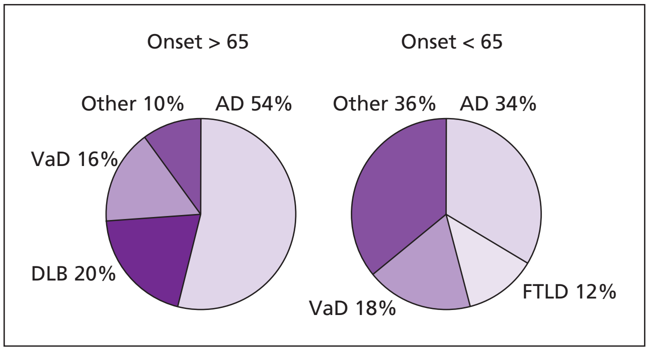

Figure 7.1 Epidemiology of dementia in older adults (onset age >65 years) and younger adults (onset age <65 years). Composite prevalence data derived from European series are displayed. The prevalence of dementia with Lewy bodies (DLB) shows wide variation between series. AD, Alzheimer's disease; DLB, dementia with Lewy bodies; FTLD, frontotemporal lobar degeneration; VaD, vascular dementia.

in Europe, for people over the age of 65 years, are approximately 6% for all causes of dementia and approximately 4% for AD. Dementia in people under the age of 65 years (young onset dementia) is increasingly recognized as an important clinical and social problem, with UK prevalence rates estimated as 67–81/100,000 in people aged 45–65 years. Although data for individual diseases are limited by diagnostic accuracy, as a group degenerative diseases are numerically the most important causes of dementia in both older and younger adults in Western countries and probably worldwide. The young onset forms of these diseases are frequently familial. Some rarer degenerative dementias such as variant Creutzfeldt–Jakob disease (vCJD) occur typically in the young patient, while other disease processes, such as fronto-temporal lobar degeneration (FTLD) and alcohol-related dementia, are also common in younger age groups. In contrast, DLB, a common cause in patients over 65 years of age, accounts for only a small proportion of young onset cases. Vascular disease is a common cause of dementia across all age groups. The epidemiology of dementia diseases in younger and older adults is presented graphically in Figure 7.1.

Cognitive functions and their clinical syndromes

Cognition, like other aspects of human brain function, has a modular organization, and different cognitive functions have distinct anatomical substrates. While a global impairment of cognitive function is often observed in delirium, specific cognitive profiles in acute brain disease are potentially of great localizing and diagnostic value. This is exemplified by the different subtypes of dysphasia in left hemisphere strokes, or the profound amnesia of Wernicke–Korsakoff syndrome. Our present understanding of the dementias has been transformed by the concept that different brain regions are affected in a characteristic and non-uniform manner as disease evolves (Table 7.2); the identification of an evolving rather than static pattern of cognitive deficits is often critical in establishing a clinical diagnosis of dementia.

Attention

Considered very broadly, attention is the ability to gate and focus sensory information and to direct awareness. The control mechanisms for attention are mediated by a hierarchy of brain structures: awareness and alertness are maintained by the ascending reticular activating system in the brainstem which projects to the thalamus and cortex; a bilateral frontal and parietal cortical network enables selective attention to particular events and types of stimuli, and divided attention to multiple events and stimuli. This cortical control system modulates activity in sensory cortices as well as the motor areas involved in response preparation. The distributed brain networks that regulate attention are vulnerable to many different disease processes. Deficits of attention are a cardinal feature of delirium, and impaired or inefficient attention is a feature of many dementias. However, the most striking deficits of attention, and those with greatest localizing value, occur with focal lesions such as stroke involving the non-dominant parietal lobe. The syndrome of hemi-neglect manifests as unawareness of contralateral (most frequently left) space. The patient may not perceive contralateral stimuli, or contralateral stimuli may be perceived when presented alone, but extinguished on presentation of simultaneous bilateral stimuli (sensory extinction). The neglect syndrome is not simply attributable to sensory deficits such as hemianopia or hemianaesthesia. Failure to direct attention to the affected field is illustrated by constructional or cancellation tasks in which stimulus features on the affected side are systematically omitted or overlooked, and there may be associated neglect of contralateral auditory stimuli that have a bilateral cortical sensory representation. Breakdown in body schema is suggested by lack of awareness of deficits involving the contralateral side of the body (anosognosia) or failure of the patient to own their contralateral limbs. The deficit may also extend to mental imagery.

Memory

Impaired memory is a defining feature of acute disorders of cognition such as the amnestic syndrome and the discrete clinical syndrome of transient global amnesia, and a very common complaint in a variety of different dementias. In order to make an accurate diagnosis, it is important to determine the nature of the memory complaint. Memory is a multi-component process supported by anatomically and functionally distinct brain networks. There is a fundamental distinction between explicit memory, the contents of which can be consciously accessed, and implicit memory, the contents of which are accessed automatically and do not depend on conscious mediation. Explicit memory has 'short-term' and 'long-term' components. In the neuropsychological sense, 'short-term' memory refers to the span for which information is retained for immediate repetition or reproduction, without rehearsal or other reinforcement (typically, less than a minute). Information that is retained for longer periods

Table 7.2 Clinical and other features in selected dementias.

Disease	Episodic memory	Visuospatial perception	Halluc	Literacy skills	Praxis	Speech prod	Speech comp	Exec	Cogn slowing	Behav	Mood	Brain MRI	EEG	CSF	Other*
Alzheimer's disease	+	+	±	+	+		±	±			±	Disprop hippo atrophy	Abn alpha		Myoclonus
Posterior cortical atrophy	±	+		+	+										
Corticobasal degeneration		+		+	+	±		±	±						Asymmetry, alien limb, EPS
FTLD:															
Fronto-temporal dementia	±					±		+		+	±				
Semantic dementia				+			+	±		±		L > R TL atrophy			
Progressive non-fluent aphasia						+		±		±		L > R peri-sylvian atrophy			
Vascular dementia	+	±		±	±		±	+	+	+	±	Vasc changes	Bitemp slowing		Strokes, brisk reflexes
Lewy body/Parkinson	+	+	+	±	±			+	+	+	±		Abn alpha		EPS Fluctuation
Huntington's disease§		±						+	+	+	+	Caudate atrophy			Chorea/other EPS, genetics
Prion disease	+	+	±	±	±			+	±	+	+	Abn BG signal	Periodic compl		Myoclonus, ataxia, rapid
Transient epileptic amnesia	+							±		±	±	Abn MTL signal/atrophy	Epilep changes		Fluctuation, seizures
Limbic encephalitis	+	±	+					±		+	+		Epilep changes	Cells, OCBs	Ca, ANAb VGKC, rapid
Cerebral vasculitis	±	±	±	±	±	±	±	±	±	±	±	Abn signal	Slowing	Cells, OCBs	Rapid
Multiple sclerosis	±							+	+	±	+	Abn wm signal		OCBs	VEPs, BAERs, abn MRI cord
Metabolic dieseases	±							+	+	+	±				Metabolic, other invest
Psychiatric disease	+		±			±		±		+	+				Fluctuation, inconsistency

+, Characteristic feature; ±, less prominent or inconsistent feature.

*Helpful but not invariable.

§Similar 'subcortical' profile of cognitive impairment in many diseases with basal ganglia involvement.

Abn, abnormal; ANAb, antineuronal antibodies; BAERs, brainstem auditory evoked responses; behav, behaviour; bitemp, bitemporal; ca, cancer; cogn, cognitive; comp, comprehension; compl, complexes; disprop, disproportionate; epilep, epileptiform; EPS, extrapyramidal syndrome; exec, executive function; FTLD, frontoemporal lobar degeneration; halluc, hallucinations; hippo, hippocampal; invest, investigations; L, left; MTL, mesial temporal lobe; OCB, oligoclonal band (especially unmatched); prod, production; R, right; vasc, vascular; VEPs, visual evoked responses; VGKC, voltage-gated potassium channel antibodies; wm, white matter.

constitutes 'long-term' memory. Long-term memory can be further subclassified into memory for episodes or events from the individual's past experience, i.e. remembering what has happened (episodic, event or autobiographical memory), and conceptual knowledge about the world, i.e. remembering what something is (semantic memory).

The selective breakdown of semantic memory is a cardinal feature of the semantic dementia phenotype of FTLD. Episodic memory can itself be further divided into operationally distinct processes: the encoding and subsequent retrieval of new events (anterograde memory); retrieval of events prior to the onset of the illness (retrograde memory); and memory for different types of material (e.g. verbal material, faces and topography).

A characteristic amnestic syndrome with severe deficits of anterograde and retrograde memory in the setting of a clear sensorium and with preserved immediate (short-term) recall was originally described in the setting of thiamine deficiency in chronic alcoholism (Wernicke–Korsakoff syndrome, Chapter 18), and subsequently in patients undergoing bilateral temporal lobe resection for intractable epilepsy (notably the much-studied patient known as H.M.) and in other conditions such as Herpes simplex encephalitis (Chapter 8). Such patients are profoundly disabled, as they are effectively marooned in the immediate present with no capacity to lay down new memories, although it may be possible to demonstrate preserved implicit memory and procedural learning. Amnestic syndromes of varying severity are common after traumatic brain injury.

Less profound and incomplete deficits of verbal, visual and topographical memory are common early in the course of AD, DLB, vascular dementia (VaD) and other diseases. Patients frequently describe an inability to recall the details of conversations and messages, and the names of acquaintances. Impaired verbal episodic memory is the most sensitive cognitive marker of early AD, although it is not specific. Impaired topographical memory commonly presents as a difficulty with route finding, and a tendency to become lost in unfamiliar locations.

The medial temporal lobes (hippocampal formation, parahippocampal gyrus and entorhinal cortex, Chapter 2) are critical for episodic memory. The diencephalic system, comprising the thalamus and its limbic connections including the fornix and mamillary bodies, and the basal forebrain also have important roles. Postmortem findings in Wernicke–Korsakoff syndrome typically include petechial haemorrhages with astrocytic degeneration in the mammillary bodies and medial dorsal thalamic nuclei. Functional imaging studies during transient global amnesia have demonstrated localized transient hypo- or hyperperfusion consistent with dysfunction of these structures and their connections. The ascending cholinergic projection pathways, which exert important modulatory and attentional influences on the medial temporal lobe and neocortex, are disrupted in cholinergic deficient disease states such as AD and DLB. Posterior cortical areas including the posterior cingulate, retrosplenial and temporoparietal association cortex are densely connected via the diencephalic system with the medial temporal lobes and have also been implicated in AD. Memory impairment in the setting of frontal lobe disease is likely to be heterogeneous and multifactorial: memory processes that may be affected include the editing of encoded material, organized search of memory stores, attribution of the source of particular memories, and possibly emotional valence.

Short-term memory comprises separate systems for the temporary storage of auditory verbal, visual and spatial information. Rather than being passively stored, information in short-term memory generally undergoes some form of cognitive manipulation, e.g. when dialling a new telephone number, making sense of an ambiguous spoken message or visualizing an unfamiliar route. These are active processes that are directed by executive systems (see below). The interaction of executive systems with short-term memory stores constitutes 'working memory'. This interaction is illustrated in the distinction between forward digit span (passive storage of information) and backward digit span (active manipulation of online material). Working memory deficits are common in acute conditions with impaired attention and have been documented in many degenerative disorders, including AD, DLB, VaD and FTLD. It is likely that verbal short-term memory is supported by a fronto-parietal network in the left cerebral hemisphere, and visuo-spatial short-term memory by a corresponding network in the right cerebral hemisphere. These short-term storage mechanisms can be regarded as 'slave' systems under the executive control of fronto-subcortical networks.

Paramnesias

The paramnesias are characterized by false or distorted recall and may occur in acute or chronic settings. The patient when prompted to fill a gap in the record of everyday experience may describe events that never occurred, or may spontaneously supply detailed accounts of events that could not possibly have occurred (confabulation). Reduplicative paramnesias are characterized by the belief that particular places or persons have been transposed or duplicated: the patient may report that their house is an exact replica of the 'real' one (topographical paramnesia), or that their spouse has been replaced by an impostor with identical appearance (the Capgras delusion, Chapter 21). Confabulatory disturbances are most often observed in the setting of frontal lobe or fronto-limbic damage.

Transient global amnesia

Transient global amnesia is a distinct syndrome characterized by the sudden onset of severe anterograde amnesia generally lasting less than 24 hours. The patient often appears bewildered, repetitively asking the same questions. There is no disturbance of alertness and, in contrast to psychogenic fugue, personal identity is retained. Procedural and semantic memory are spared (e.g. the person may carry on driving or perform occupational tasks competently during the episode), other cognitive functions are intact and the neurological examination is normal. Complete recovery with amnesia for the period of the episode and a variable retrograde time-span is usual, although there may be persistent subtle memory deficits, and recurrence is rare. The condition generally occurs in later life. There are a number of associations, including physical exertion, exposure to cold, strong emotion, sexual activity and migraine; however, in the substantial majority, the aetiology remains unclear. Investigations are indicated to exclude mimics such as temporal lobe lesions, but are generally unrevealing. Recurrent attacks, especially on waking from sleep, suggest the syndrome of transient epileptic amnesia (Chapter 6), often accompanied by interictal memory impairment; this is an important differential diagnosis of dementia.

Perception

Perceptual analysis of the environment is a complex multi-stage process. Visual processing is the most widely studied modality and in general the most clinically relevant. The processing of visual objects involves dissociable stages of early sensory analysis, formation of structural representations and the association of those representations with meaning. Objects have locations in space, and the perception of space requires specific neural mechanisms. The mechanisms that process visual objects and visual space can be damaged selectively, supporting a broad anatomical and physiological distinction between ventral 'what is an object' and dorsal 'where is an object' cortical processing streams (Chapter 2). Selective impairments of visual functions such as motion detection (akinetopsia) and colour perception (achromatopsia) have been described with posterior circulation strokes and other focal lesions involving the cortical visual pathways in the posterior cerebral hemispheres (Chapter 13). These syndromes may be transient or appear during the recovery phase of a more extensive visual deficit. Syndromes of progressive visual dysfunction are associated with relatively focal tissue loss and metabolic derangements involving the posterior cerebral hemispheres, and are often classified together on anatomical grounds as the posterior cortical atrophies (PCA). The most frequent tissue pathology is AD; however, a variety of others are represented, including cortico-basal degeneration (CBD), DLB and prion disease.

Cortical blindness may result from bilateral occipital lobe damage and involvement of lateral occipito-parietal areas may be associated with denial of blindness or visual anosognosia (Anton syndrome). Partial forms of cortical blindness affecting visual acuity, stereopsis or the discrimination of elementary visual patterns (form, colour or motion) also occur in PCA. Clinically, such deficits may mimic peripheral visual loss: patients may complain of blurred vision, decreased acuity or desaturation of colours. Letters of similar shape may be confused. Difficulties may be particularly apparent under conditions of reduced contrast or changing illumination. Misperceptions of visual information may occur; patterns on fabric or wallpaper may seem to shift and change, objects in the environment or body parts (especially faces) may appear distorted (metamorphopsia), abnormally persistent or transposed (palinopsia), or multiply reduplicated (polyopia).

Identification of visual objects may be impaired despite intact early visual processing. The patient may fail to recognize common household items or familiar people. There may be difficulty in distinguishing coins, banknotes or playing cards, and on examination the patient may be unable to identify fragmented, distorted or overlapping pictures or letters, silhouettes or unusual views. Such patients have apperceptive visual agnosia: this means an inability to form structural representations of visual objects, the distinctive geometric and volumetric features that enable object identity to be abstracted despite changing contexts and viewpoints. The anatomical substrates of early visual processing and object representation are likely to involve a cortical pathway extending from early visual cortices into parieto-occipital association areas. This pathway is vulnerable to various disease processes, such as infarcts, hypoxic damage and focal degeneration in PCA. Processing of complex objects such as faces involves the ventral 'what' visual stream in the inferior temporal lobe, including the 'fusiform face area'. Damage involving this region may lead to impaired face perception (prosopagnosia).

Deficits in the perception of visual space are more common than selective disorders of visual object processing. These deficits interact with mechanisms for spatial attention, which are generally more severely affected in focal brain lesions such as stroke involving the parietal lobes. However, visuo-spatial deficits are often prominent in dementias affecting the posterior cerebral hemispheres such as AD and DLB. Visuo-spatial disorders can be broadly classified as visual disorientation, the impaired perception of space relative to self (egocentric space), and visuo-spatial agnosia, the impaired perception of spatial configurations that are not referenced to one's own position (exocentric space). Patients with visual disorientation may be unable to locate objects such as cutlery immediately after they are put down or when the item is in front of them, and typically misreach for items. Threading a needle, reading lines of text, writing, using an index or even keeping within traffic lanes when driving may become impossible. Accidents when walking or driving are common, because of loss of the ability to judge distances or motion. Ultimately, such individuals become functionally blind. On examination, these patients have components of Balint's syndrome: fragmented perception of the visual field (simultanagnosia), inability to perform visually guided movements (optic ataxia) and/or inability to direct the eyes to a point in space (ocular apraxia). Because of the retinotopic encoding of egocentric space, these deficits frequently resemble hemi- or quadrantanopic field defects.

Patients with visuo-spatial agnosia may be unable to orient clothing when dressing, a camera when taking a photograph or an envelope when posting a letter. Loss of the ability to tell the time from a clock is characteristic. Patients are commonly unable to navigate familiar routes, and become lost in the neighbourhood or even within their own house (topographical disorientation). Skills such as reading text or maps, writing and calculation, which depend on accurate perception of spatial patterns, are often degraded. On examination, copying and constructional tasks are poorly performed and there may be specific deficits of spatial discrimination or spatial search (such as counting dots in an array). Anatomically, visuo-spatial deficits are associated with damage to the superior and posterior parietal lobes, within the dorsal cortical 'where' visual processing stream.

Perceptual defects in cognitive disorders are not confined to the visual domain. Cortical deafness is a rare accompaniment of bilateral damage involving auditory cortex and ascending auditory pathways, and auditory agnosia for complex sounds such as music and environmental noises may occur with diseases involving either temporal lobe. Loss or distortions of taste (dysgeusia) occurs with damage involving the gustatory pathways and cortex in the region of the insula. Olfactory identification deficits may occur early in the course of AD, Parkinson's disease and other degenerative dementias, and are likely to be at least partly central in origin. Disorders of cortical somatosensory function such as impaired perception of shape (astereognosis) and spatial configurations on the body surface (such as drawn numbers: agraphaesthesia) and impaired recognition of objects by touch (tactile agnosia) may occur with both acute damage involving the parietal lobes and in degenerative conditions such as CBD.

Hallucinations

Hallucinations are perceptual experiences in the absence of an external sensory stimulus. They may occur in normal individuals under conditions of fatigue or sensory deprivation, or at the onset of sleep (hypnagogic hallucinations). In organic brain disease, hallucinations occur most commonly in the visual modality, and are a frequent feature of delirium. However, hallucinations in other disease states and in non-visual modalities are well recognized (e.g. olfactory hallucinations in temporal lobe epilepsy). Complex verbal (auditory) hallucinations are typical of psychiatric disorders such as schizophrenia but distinctly unusual in organic disease. Visual hallucinations can arise from a variety of insults at different stages of the retino-calcarine and cortical ventral visual pathways. Hallucinations may arise from two general mechanisms: abnormal release of sensory cortex because of loss of sensory inputs from the periphery or other regulatory controls, or abnormal excitation or disinhibition of sensory cortex by irritative processes such as seizures or migraine. Deafferentation of early visual cortex in the setting of peripheral visual loss may be associated with isolated well-formed visual hallucinations in the absence of cognitive decline (Charles Bonnet syndrome). An analogous auditory mechanism may produce musical hallucinations in acquired deafness. Damage involving the ventral midbrain may produce vivid 'dream-like' peduncular hallucinations of cartoon-like images or complex scenes, resulting from dysfunction of the reticular activating system. Structural or functional lesions involving early visual cortices may produce elementary visual hallucinations (exemplified by 'fortification spectra' or teichopsia in migraine) while more complex or multimodal hallucinations, sometimes involving distortions of self-perception, may occur in the setting of temporal lobe disease.

Visual hallucinations are modulated by dysfunction of neurotransmitter pathways. Hallucinations are particularly striking and complex in diseases such as DLB in which there is a cortical deficiency of acetylcholine. Descriptions of hallucinations are often remarkably stereotyped: the patient typically sees unfamiliar people or animals (especially cats or other small creatures), mobile or stationary, often multiple, but generally silent. Hallucinations frequently appear in the evening or in darkness. They may be glimpsed transiently at the edge of view, or emerge from an environmental feature such as a piece of furniture or a garden scene. Extracampine hallucinations are associated with the sense of a presence beyond the field of view. The 'phantom boarder' delusion (the sense that there is another person in the house when there is not) may be a related phenomenon.

Knowledge

The brain mechanisms that mediate the storage and retrieval of knowledge constitute those of semantic memory. The most striking and selective deficits of knowledge are produced by focal lesions involving the ventral visual pathways in the inferior temporal lobes and by focal degeneration of the left temporal lobe in semantic dementia (SD). In SD, disintegration of word knowledge produces a progressive impairment of word-finding and word comprehension which is generally the presenting and most prominent feature of the syndrome. Naming deficits are characteristically early and prominent; a generic or superordinate term is often used in place of the more specific one (e.g. 'animal' in place of 'camel'). These patients do not grasp the meaning of words and typically have particular difficulty with definitions.

The selective inability to associate visual representations of objects with meaning constitutes an associative visual agnosia, which may occur as a relatively isolated deficit with temporo-occipital lesions or may develop in the course of SD. As is the case for verbal knowledge, semantic deficits can be relatively specific for the visual domain. Patients may be unable to identify everyday objects or describe their function despite accurate and detailed analysis of perceptual features. Patients with prosopagnosia lose the ability to recognize familiar faces, including acquaintances, famous people or even close family members. The recognition deficit may be selective for faces, dissociating from other types of person knowledge and from other categories of knowledge.

Neocortical regions in the anterolateral and inferior temporal lobes are likely to be critical for conceptual knowledge. Impaired word knowledge in SD is associated with atrophy involving the dominant (left) anterolateral temporal lobe. Person knowledge is likely to be asymmetrically distributed between the right and left anterior temporal lobes, the left anterior and inferolateral temporal lobe representing verbal information (such as personal names) and corresponding regions of the right temporal lobe representing familiar face information. Progressive prosopagnosia has been described much less frequently than SD. This is likely to be at least partly attributable to the clinical silence of the right temporal lobe relative to the eloquent left temporal lobe.

Voluntary action

Diseases that disturb the cognitive control processes involved in programming and guiding voluntary action produce apraxia: a disturbance of voluntary movement that cannot be explained by elementary motor or sensory deficits. The classification of apraxia poses conceptual and practical difficulties; however, a basic distinction can be drawn between disorders that affect unfamiliar, novel or meaningless actions (ideomotor apraxia), and disorders that affect previously learned actions (ideational apraxia). Apraxia generally occurs in association with more widespread deficits involving the dominant parietal or frontal lobes; however, cases of primary progressive apraxia have been described.

Apraxia for novel and meaningless actions is a prominent feature of dementias such as AD that involve the posterior hemispheres, and in this setting there is often additional evidence of impaired visuo-spatial perception. Novel tasks requiring mechanical problem-solving (such as assembling prefabricated furniture or models) and learning new motor skills pose particular difficulties. The patient has difficulties in imitating the examiner's meaningless hand positions. There may be particular difficulty when movements must be combined into a short sequence.

Less commonly, apraxia leads to impaired production of actions previously learned. Manual occupations and hobbies may be abandoned, and the patient may be unable to use common household tools and utensils, or attempt to use them inappropriately (e.g. attempting to write with scissors). When instructed to perform a symbolic gesture (such as waving goodbye or saluting) or to pantomime the use of a tool (such as a screwdriver or hammer) an awkward or fragmentary approximation may be produced. Both the configuration of the fingers and the movements themselves are typically abnormal. Action production may be facilitated by holding the corresponding tool or other contextual cues. In addition, the patient may fail to recognize familiar gestures mimed by the examiner.

Apraxias affecting specific parts of the body are well recognized. Asymmetric limb apraxia is a cardinal presenting feature of CBD, where it is characteristically accompanied by asymmetric rigidity and other extrapyramidal or cortical sensory signs. Actions involving the affected limb comprise coarse, uncoordinated or mutilated constituent movements, sometimes termed limb-kinetic apraxia. Impairments affecting the voluntary control of orofacial movements often dissociate from disorders of limb praxis. Orofacial apraxia is often observed in association with impaired speech production. The patient may lose the ability to whistle and may complain of difficulty initiating chewing or swallowing. When instructed to cough, yawn or sigh the patient may produce an inadequate facsimile or simply repeat the instruction emphatically; however, these actions are typically normal when performed spontaneously and the examiner's orofacial gestures may be imitated competently.

So-called constructional apraxia, impaired ability to copy drawings of objects or designs, is observed both with focal lesions and degenerative diseases variously affecting visuo-spatial perception, spatial attention and executive processes. In the majority of cases it is likely to be multi-factorial in origin rather than representing a specific disorder of voluntary action. Similar reservations apply to several other disorders, including dressing apraxia which is probably largely attributable to deficient visuo-spatial analysis, and apraxia of eyelid opening which in many cases has the features of a focal dystonia. The true status of gait apraxia, the selective impairment of walking (and often other axial motor programmes), remains somewhat controversial, as gait abnormalities may arise at various levels of the motor hierarchy. However, it is observed in association with focal lesions and degenerative processes affecting the frontal lobes and subcortical projections (as in hydrocephalus).

Patients with asymmetric limb apraxia may have difficulty in making cooperative movements using both hands because the more affected hand tends to mirror the other or otherwise interferes with the action: the alien limb phenomenon. The patient may complain that the affected arm is useless or seems not to belong to them, and the arm may tend to levitate or assume other odd postures (especially when attention is diverted or during walking). Forced grasping or reaching for objects in the immediate environment may occur, or there may be more organized purposeless actions such as repeatedly removing and replacing spectacles. Among the dementias, the most characteristic association is with CBD, although other pathologies have been described.

The neural control mechanisms for the control of voluntary action are distributed within a network of cortical and subcortical areas, and mixed forms of limb apraxia are common. Conceptual knowledge of gestures is likely to be mediated at least in part by the dominant temporal lobe, while the left parietal lobe is likely to have a key role in the integration of sensory information in the organization of actions. An anterior system for the production of gestures may represent motor programmes for action in each hemisphere, and predominantly unilateral damage involving this system may lead to asymmetric limb-kinetic apraxia involving either side. Orofacial apraxia is associated with focal lesions or degenerative syndromes (such as progressive non-fluent aphasia) with asymmetric atrophy predominantly involving left inferior frontal and opercular regions.

Speech

The complex operations of human speech can be broadly classified as sensory decoding, comprehension, repetition, retrieval and production. Each of these operations can be considered at the level both of single words and sentences. These different operations are affected in a variety of acute and chronic cognitive disorders. Speech and language impairments (the dysphasias) are most commonly the result of focal lesions affecting the cortex of the dominant (left) cerebral hemisphere, but the recent recognition of focal 'language-based' dementias has revolutionized contemporary thinking about the degenerative brain diseases. Classic concepts of the human language system such as that of Lichtheim posited a cortical centre for word concepts connected by transcortical pathways with a posterior centre for processing word sounds and an anterior centre for programming speech output (Chapter 3). This model has undergone considerable refinement in recent decades, influenced by functional imaging studies in healthy individuals as well as clinical observations in both stroke and focal cortical degenerations. The basic bedside distinction between fluent ('Wernicke's', 'sensory', 'posterior') and non-fluent ('Broca's', 'motor', 'anterior') dysphasia remains useful; however, it is not absolute clinically, anatomically or pathologically. Because of its quite different anatomical and clinical significance, it is important to distinguish fluent dysphasia from confusion (e.g. in the context of delirium); this can usually be accomplished by a careful analysis of the patient's spontaneous speech, in particular the presence of speech errors (paraphasias).

Comprehension of speech depends fundamentally on the accurate decoding of the acoustic signal at the level of its constituent sounds. In the setting of acute disease such as stroke, impaired speech comprehension or Wernicke aphasia is generally associated with damage involving Wernicke's area in the dominant posterior superior temporal lobe. However, the true functional and anatomical status of this area remains contentious. Selective impairments of speech perception manifesting as word deafness have been described rarely with acute bilateral or left-sided damage and degenerative disease affecting the posterior temporal lobe. Such patients have difficulty both in understanding and repeating spoken words despite normal comprehension of written material. Impaired comprehension of single words in the setting of intact acoustic analysis and repetition constitutes a transcortical sensory aphasia (Chapter 3), originally described with posterior watershed infarcts. However, a similar syndrome is associated with breakdown in verbal knowledge systems in SD (see below), suggesting an important role of the left anterior temporal lobe in normal language processing which is more difficult to reconcile with classic models of language organization derived from the study of stroke and other acute lesions. Impaired sentence comprehension occurs in dementias such as progressive non-fluent aphasia (PNFA) in which there is disturbed processing of grammatical structure. Functional disconnection of posterior (input) from anterior (production) language areas produces a selective impairment of speech repetition or conduction aphasia, observed chiefly with focal damage involving the left parieto-temporal junction and the arcuate fasciculus.

Impaired word retrieval leads to word-finding pauses or circumlocutions in everyday conversation and a reduced ability to name (anomia). It is most often studied using confrontational naming tasks, in which nouns must be produced in response to pictures or other stimuli. Failure of retrieval in this situation is characteristic of anomic aphasia, which may be associated with a variety of focal lesions affecting the language system, e.g. during the recovery phase of stroke. Progressive anomia is a hallmark of SD; however, naming (and, more generally, word retrieval) deficits are also observed in AD and many other dementias. It is important to appreciate that confrontational naming depends on many distinct subprocesses, including intact perception and executive function, and intact connections between the cortical areas mediating these functions. This is illustrated by naming impairment resulting from visuo-perceptual deficits in PCA, and modality-specific impairments (e.g. optic and tactile anomia) with focal lesions interrupting transcortical and interhemispheric sensory pathways. Normal propositional speech involves not simply the retrieval of individual words, but the construction of a sentence that conveys an idea or message. Disruption of the process of message generation produces dynamic aphasia, with characteristics similar to transcortical motor aphasia: reduced spontaneous propositional speech despite the ability to produce speech relatively normally in specific contexts such as naming, repetition or reading. Dynamic aphasia has been documented with focal lesions and dementias that damage frontal or fronto-subcortical circuitry.

The spoken output of words and sentences in turn requires a number of distinct operations. The components of the verbal message must be combined according to morphological and syntactic rules. The breakdown of grammatical output (syntax) is a hallmark of Broca's aphasia, observed classically with focal lesions involving the inferior frontal gyrus of the dominant hemisphere. As is the case with Wernicke's area, however, the true functional role of Broca's area has not been fully clarified and should not be equated simply with language output. Broca's aphasia is characterized by effortful, dysfluent and agrammatic speech with a disjointed and telegraphic quality because of omission of verbs, prepositions and other function words. The production of single words involves both the selection and grouping of appropriate syllable codes (phonology) and the articulation of the corresponding motor programme. Progressive breakdown in either or both of these operations commonly occurs in PNFA, and in other disorders such as CBD and motor neurone disease dementia. This syndrome includes relatively pure cases of cortical anarthria. Phonemic paraphasias (such as 'stirel' for 'squirrel') are often accompanied by articulatory errors. Prosody, the pattern of stress and timing that constitutes the melody of speech, is frequently abnormal. It is also important to distinguish dysfluency resulting from a primary disorder of speech production from interrupted output resulting from prolonged word-finding pauses (so-called 'logopenic' aphasia), which may occur in other conditions including AD. The spontaneous production of novel non-words (neologisms) and jargon may accompany fluent aphasia in acute disorders but rarely in degenerative disease.

Disorders that produce selective impairments of speech processing are associated with focal lesions or asymmetric atrophy predominantly involving the left perisylvian region. Deficits of speech perception are associated with damage involving the left posterior superior temporal gyrus, a region that includes early auditory areas. Impaired syntactic comprehension has been correlated with involvement of the left posterior temporo-parietal region. Impaired word retrieval occurs with interruption of a distributed asymmetric (predominantly left-sided) brain network including left lateral temporal cortex, left inferior and lateral frontal areas. Partially overlapping regions including the left inferior frontal gyrus, frontal operculum and anterior insula have been identified in group and single-case studies of speech production breakdown in stroke, PNFA and other disorders, implicating these dominant anterior regions in the motor programming of speech. The basal ganglia, thalamus and subcortical pathways in the dominant hemisphere participate in distributed cortico-subcortical networks mediating language and speech, and focal lesions involving these structures may closely resemble the corresponding cortical functional deficit.

Literacy and numeracy

An individual's premorbid level of literacy and numeracy is heavily influenced by educational attainment and potentially by specific long-standing limitations such as developmental dyslexia or dyscalculia. Such factors must be taken into account when interpreting the effects of disease.

A basic distinction is often made between reading disorders that occur without writing impairment (alexia without agraphia) and those that are accompanied by writing impairment (alexia with agraphia), originally described with acute lesions such as stroke affecting the posterior cerebral hemispheres. Alexia without agraphia is classically produced by the conjunction of a right homonymous hemianopia and damage involving the posterior corpus callosum, precluding the transfer of information from the left hemi-field (right occipital lobe) to the verbal left hemisphere; alexia with agraphia results from more extensive lesions involving the posterior left hemisphere. An alternative classification of the dyslexias is based on the cognitive operations involved, whereby disturbed visual analysis of written words produces a peripheral dyslexia (often with preserved writing ability) and disturbed analysis of written words for sound or meaning produces a central dyslexia (often with associated deficits of written output). Impaired visual analysis of written words or peripheral dyslexia is often a prominent feature of PCA, in which associated visuo-perceptual and visuo-spatial impairments are common. These individuals typically read letter by letter. Central deficits of written word processing beyond the stage of visual analysis fall into two general categories, which may dissociate: these correspond to two parallel routes to reading, based on analysis for sound (the phonological encoding of print-to-sound correspondences) and analysis of meaning (sight vocabulary). If reading by sound is damaged, there is a failure to use the general rules of phonological encoding (phonological dyslexia). These patients have particular difficulty reading meaningless words, grammatical function words (e.g. 'and', 'if', 'for') and morphological features such as tense or plurals. If reading by sight vocabulary is damaged (surface dyslexia), there is reliance on reading by sound. Irregular words are incorrectly regularized according to surface orthographic features (e.g. 'yacht' may be pronounced 'yached'), while regular words are read correctly. Impaired reading by sight vocabulary is a frequent and characteristic feature of SD.

Visually based (peripheral) dyslexia is associated with bilateral or predominantly left-sided occipito-temporo-parietal damage or hypometabolism and histopathological involvement of the ventral visual pathway. In central dyslexia, impaired reading by sight vocabulary is associated chiefly with degeneration of the left anterior and inferior temporal lobe, in common with other components of the SD syndrome, while impaired reading by sound is associated with pathology in left peri-sylvian language regions.

Impairments of writing and spelling (the dysgraphias) can be broadly classified according to whether the core defect lies with spelling processes (central dysgraphias) or the motor programming and execution of writing (peripheral dysgraphias). As is the case for the dyslexias, mixed forms are common. Spelling can proceed via sound-based (phonological) and vocabulary-based routes, and central dysgraphias affecting each route have been described in patients with dementia. Impaired spelling by sound (phonological dysgraphia) is associated with particular difficulty writing grammatical function words and word endings. The breakdown of vocabulary-based spelling (surface dysgraphia) manifests as regularization errors in rendering exception words (e.g. 'juice' may be spelled 'juse') while phonologically regular words are spelled correctly. Impaired spelling vocabulary is a characteristic feature of the SD syndrome, but also occurs commonly in AD and in other dementias. The various stages of letter shape selection, formation, placement and sequencing that underpin the motor output process of writing may be deranged in disease processes that disrupt visuo-spatial analysis or voluntary action. Dysgraphia is generally a feature of diseases involving the left parietal lobe; however, surface dysgraphia is associated with surface dyslexia and other features of SD in the setting of left temporal lobe atrophy.

Disorders of calculation can be classified according to whether the core defect lies with computation proper or with the procedures required to process written and spoken numbers. Patients typically complain of a loss of facility in handling change or household accounts, and may have relinquished these responsibilities to others. There may be specific difficulties in adding scores and calculating totals in games, in using measuring instruments, or in reading and writing numerals and number words (e.g. when issuing a cheque). Like dysgraphia, dyscalculia is often a prominent feature of diseases affecting the dominant parietal lobe. The association of dysgraphia and dyscalculia with finger agnosia and right–left disorientation is known as Gerstmann's syndrome (Chapter 3) although it is unlikely this particular constellation has special significance other than implicating the dominant angular gyrus.

Executive function

The generation of complex behaviour demands that many cognitive operations are combined, coordinated, adapted to different contexts and directed to relevant goals. The regulatory and supervisory brain mechanisms that achieve this together constitute the cognitive executive. These mechanisms are instantiated chiefly in frontal lobe cortex and its subcortical connections, and indeed the recognition that frontal lobe damage may produce profound alterations in conduct and personality (as in the celebrated case of Phineas Gage) was one of the cornerstones of modern behavioural neurology. However, it is important to recognize that executive dysfunction and frontal lobe impairment are not equivalent concepts. The cognitive and anatomical organization of the executive remains poorly understood: while it is possible to identify broad syndromes of executive dysfunction, in clinical practice these almost invariably overlap. Executive impairments are produced by a very wide range of acute and chronic diseases.

Perhaps the most striking frontal lobe syndrome is characterized by loss of capacity to gate or modulate the effects of cognitive inputs according to the overall context. Patients with impaired response modulation have particular difficulty in taking account of feedback or assessing the consequences of their own behaviour. Affected individuals almost invariably lack insight into their difficulties, but a change in the patient's personality is all too evident to others, and is accompanied by poor social judgement and inappropriate behaviour or insensitive remarks. Disinhibition and impulsivity may disrupt personal and occupational relationships. There is a reduced capacity for abstract thought, and patients typically display an inflexible and concrete approach to occupational and daily life tasks. Defective processing of social signals may contribute to impaired understanding of the mental states of self and others ('theory of mind'). Checking or counting routines, ritualized daily routes and schedules, clock-watching and hoarding are common. Analogies and similarities may not be recognized, and proverbs interpreted literally ('People in glass houses shouldn't throw stones or the glass will break'). The ability to formulate a strategy for searching cognitive or sensory inputs is often compromised: this commonly manifests as reduced verbal fluency (the number of words generated in 1 minute according to a specified criterion, usually semantic category or initial letter).

An impaired ability to generate behavioural outputs leads to a loss of autonomy and increasing dependency on environmental cues and events to initiate behavioural subroutines. Apathy (abulia), inertia, passivity, perseveration, and motor and verbal stereotypies are common features of this syndrome. Left undisturbed, patients may contentedly spend all day watching television or absorbed in jigsaw puzzles or word games, and they may be disengaged from these activities only with difficulty. Loss of initiative commonly extends to household tasks and personal hygiene. There may be utilization behaviour (e.g. the patient may don spectacles or peel a piece of fruit automatically when the item is placed before them), hyperorality (sometimes including mouthing of inedible items) or mimicry of others' speech (echolalia) or actions (echopraxia).

Slowness of thought (bradyphrenia) and difficulty in switching between behavioural subroutines or 'sets' spontaneously or according to context are hallmarks of fronto-subcortical damage. There may be perseverative errors on attempting to draw a sequence of alternating shapes or produce a sequence of alternating hand movements. Palilalia (repetition of the patient's own words or terminal phrases) also occurs.

Executive difficulties are exposed by tasks that demand planning, abstract thought, flexibility and consideration of alternative solutions. There is often little consistency between tests or even between testing sessions in the individual patient. Characteristic features include implausible but over-precise estimates (distance from London to New York is '266 miles'), impaired performance on dual tasks (such as tracking a visual target while reciting a list of numbers), and difficulty grasping simple rules (sorting multidimensional items by size, shape or colour) or in devising a problem-solving strategy (such as the 'Tower of London' puzzle).

The anatomy and pathophysiology of executive dysfunction remains poorly understood, and there is little consensus regarding the neural correlates of core executive functions. A similar pattern of cognitive and behavioural impairments may be associated with variable findings on structural and metabolic brain imaging. Disinhibition, sociopathic behaviour and altered physiological drives broadly correlate with predominantly right-sided anterior temporal and inferior frontal lobe damage and hypometabolism, and abulia with dorsolateral frontal and anterior cingulate involvement. Disinhibition, impaired theory of mind and disturbed modulation of sensory inputs are associated particularly with orbitofrontal and ventromedial frontal damage.

Emotion

Alhough they have traditionally been regarded as the domain of the psychiatrist, disturbances of emotion comprehension and expression are integral to many neurological disorders and are often closely allied with other behavioural and executive impairments. Defective processing of emotions often has major social consequences. Poor understanding of the emotional states of people and animals, lack of empathy and reduced expressivity are often interpreted as coldness and lack of affection. Other patients display fatuous and puerile emotional responses. Paradoxically, there may be increased engagement with religious, philosophical or artistic pursuits. A dramatic illustration of the breakdown of normal emotion processing is the Klüver–Bucy syndrome, originally described in monkeys following bilateral temporal lobe ablation. The syndrome has been reported rarely in humans, but does occur in the context of acute destructive processes such as herpes simplex encephalitis, and is characterized by loss of normal emotional reactivity, abulia, altered sexual responses and hyperorality.

Disturbances of mood (in particular, depression and dysphoria) are commonly associated with stroke, temporal lobe epilepsy and head injury, and with AD and other degenerative disorders (Chapter 21). These affective changes are likely to be caused, at least in part, by damage involving limbic circuits and their neocortical projections. Specific deficits of emotion comprehension have been documented in both acute and chronic disorders with mesolimbic damage, and are a hallmark of certain degenerative diseases, notably FTLD and Huntington's disease. A distributed predominantly right-sided fronto-temporal network including the amygdala and orbitofrontal cortex is likely to be critical for normal emotion processing: this network is a plausible interface between primitive emotional states linked to biological drives and the neocortical cognitive machinery of complex goal-directed behaviours.

Investigation of the patient with cognitive impairment

Basic principles

The differential diagnosis of delirium and dementia is very extensive (Table 7.1), and a structured approach to the investigation of cognitive impairment is therefore essential. This approach should be tailored to the clinical problem at hand, guided by an accurate and complete history and examination (Tables 7.1 and 7.2). However, the first priority of investigation in every patient is to exclude a reversible condition. Most causes of delirium and a number of causes of dementia fall into this category, and delirium frequently supervenes on a background of more insidious cognitive decline in elderly patients and those with limited cognitive reserve. Accurate diagnosis, particularly in dementia, may have important implications for prognosis and possibly genetic counselling of other family members.

Initial investigation

Initial investigations should be minimally invasive and directed toward the identification of reversible metabolic, infective, inflammatory and other systemic processes. A number of investigations are relevant in the initial approach to both acute and chronic impairment, especially where the precise time course is difficult to establish or more than one process is likely (Tables 7.3 and 7.4). A basic initial battery includes full blood count and differential, biochemistry including serum calcium, renal, liver and thyroid function tests, coagulation profile, serum B_{12} and folate, inflammatory markers (ESR and CRP), an autoimmune screen (antinuclear factor), a chest radiograph, ECG and urinalysis. Clinical judgement is required in interpreting the significance of such screening results, e.g. a low serum B_{12} is common in the elderly, but it is rarely the sole cause of cognitive decline.

Neuropsychometry

Neuropsychometry is an extension of the bedside cognitive examination and can be very valuable in characterizing the cognitive profile in more detail (in particular, the identification of subclinical deficits that might not be volunteered in the history). It is most useful and relevant for the detection of change in cognitive function, either in assessing the effect of static insults, where ongoing deterioration is a diagnostic issue (typically, in the identification of dementia) or in assessing response to therapy. Many neuropsychometric tests provide quantitative and normative data that allow the individual's premorbid cognitive attainment to be estimated and their current cognitive performance to be measured in relation to a healthy age-matched population. Documentation of performance in particular cognitive domains allows the likely origin of the cognitive problem to be specified, because particular patterns of deficit have localizing value (Table 7.2). A plethora of neuropsychological tests is available. These require a trained neuropsychologist to administer and interpret, ideally informed by a clinical summary that identifies the purpose of the referral and areas of chief concern. The timing of test administration should be considered carefully: it is rarely informative to perform neuropsychometry during a delirium or the acute phase of a stroke or head injury (because further alteration

Table 7.3 An approach to investigation of the patient with rapid onset cognitive impairment.

Associated features	Investigations
	Screening investigations
May have systemic symptoms and signs	Blood: full blood count, renal function, electrolytes, liver function, coagulation, glucose, thyroid function, ammonia, amylase, ESR/CRP, ANF urinalysis ECG, chest X-ray
	Additional investigations
Head injury, signs of raised ICP, focal cognitive deficit, neurological symptoms and signs, no systemic explanation, neurological assessment unreliable, headache, meningism, fever	Brain imaging: CT, MRI, MRI venography, angiography CSF examination, including cultures and viral PCR, septic screens, serology vasculitis screens, neoplasia screens
Recurrent attacks suspicion inherited disease	EEG, echocardiogram autoimmune, thrombotic screens, urinary catecholamines, serotonin metabolites, porphyrins, consider specialized metabolic screens
Drug use/possible toxic exposure	Rationalize medications Drug/toxicological screens
Poor nutrition	Nutritional screens
Pain sensory/sleep deprivation environmental factors	Identify source
Major affective disorder, psychosis not attributable to above; fugue state, factitious disorder	Psychiatric evaluation

ANF, antinuclear factor; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalography; ESR, erythrocyte sedimentaion rate; ICP, intracranial pressure; MRI, magnetic resonance imaging; PCR, polymerase chain reaction.

Table 7.4 An approach to investigation of the patient with dementia.

Associated features	Investigations
	Screening investigations – all patients
May have systemic symptoms and signs	Blood: full blood count, renal function, electrolytes, liver function, coagulation, glucose, thyroid function, ESR/CRP, ANF, syphilis serology, B_{12}, folate, urinalysis
	ECG, chest X-ray, brain imaging: CT, MRI if available
	EEG
	Additional investigations – selected patients
Young onset, non-cognitive neurological features, family history	HIV serology, copper studies, slit lamp examination, consider specialized metabolic and genetic screens, muscle/axillary skin, marrow, liver biopsy
Rapid course, headache, meningism, fever other features atypical of common degenerations (including age <65, systemic features, neurological signs)	Vasculitis, auto-antibody screens (incl ANCA, APL, VGKC Ab, coeliac screens) antineuronal antibodies, other neoplasia screens (incl whole-body PET, CT)
	CSF examination (including cells, protein, glucose, oligoclonal bands, cytology, cultures; may include 14-3-3, S100, Whipple PCR, JC/other viral PCR, cryptococcal Ag, measles Ab, syphilis serology, TB and other special cultures)
	MRI FLAIR sequences, prion genotyping if suspect prion disease, tonsillar biopsy if suspect vCJD
Clinical seizures prominent fluctuation (not in context of DLB)	Prolonged EEG (if routine EEG not diagnostic) autoimmune, thrombotic screens echocardiogram, other vascular screens urinary porphyrins
Sleep disorder	Sleep study
Drug use/possible toxic exposure	Rationalize medications drug/toxicological screens
Poor nutrition, suspicion of deficiency	nutritional screens
Major affective disorder, psychosis not attributable to above; fugue state, factitious disorder	Psychiatric evaluation
Suspicion of treatable (inflammatory) process when diagnosis not established by non-invasive means	Brain biopsy

Ab, antibody; Ag, antigen; ANCA, antineutrophil cytoplasmic antibody; ANF, antinuclear factor; APL, antiphospholipid antibody; DLB, dementia with Lewy bodies; FLAIR, fluid-attenuated inversion recovery; PCR, polymerase chain reaction; PET, positron emission tomography; vCJD, variant Creutzfeldt–Jakob disease; VGKC, voltage-gated potassium channel antibody.

in cognitive state can be anticipated), or repeatedly within a short timeframe (because practice effects are likely to make interpretation difficult). The patient's age and level of education must always be taken into account and, as with any investigation, results should be interpreted in the context of the specific clinical scenario.

Brief mental state schedules such as the 30-point Mini Mental State Examination (MMSE; the Folstein test) are simple to administer at the bedside and give an overall snapshot of cognitive performance, but lack sensitivity for the detection of subtle or isolated cognitive deficits while depending heavily on particular domains, notably verbal processing. Such schedules may be of most value in charting change in cognitive function over time, although they remain crude indices. Frequently used standardized tests include the National Adult Reading Test (NART), which provides an index of premorbid intellectual attainment, and the Wechsler Adult Intelligence Scale (WAIS; revised, WAIS-R), which provides a profile of a range of verbal and non-verbal abilities. A variety of quantitative memory tests are in use, including the Recognition Memory Test for words and faces, which provides measures of verbal and non-verbal material-specific memory. Many tests have been used to assess executive function, including the Wisconsin Card Sorting Test (which requires the classification of stimuli according to various implicit rules) and Raven's Progressive Matrices (a test of abstract pattern continuation that does not depend on verbal mediation); however, this is a notoriously difficult domain to quantify and results are heavily affected by deficits in other domains (e.g. visual perception). Batteries to assess other functions such as visual object and space perception, praxis, naming and semantic knowledge are widely available.

Brain imaging

Structural brain imaging is indicated in all patients with dementia, and in patients with delirium where no systemic cause is identified, or where focal cognitive or neurological signs, headache, evidence of raised intracranial pressure or head trauma are present. This may be particularly critical in situations where neurological status cannot be reliably assessed, e.g. in acute alcohol or drug intoxication, or where an acute process may have supervened on pre-existing cognitive impairment. CT is widely available, and is adequate for detection of hydrocephalus and focal intracranial lesions such as subdural haematoma, brain abscess and tumours. CT is specifically indicated for detection of subarachnoid haemorrhage or intracranial calcification. However, magnetic resonance imaging (MRI) is distinctly superior for examination of the brainstem and posterior fossa structures, the basal ganglia and detail of cerebral white matter and the cortical mantle. In patients with dementia, T1 MRI sequences can be particularly valuable in detecting pathological atrophy: volumetric MRI employing thin slices can be used to delineate patterns of regional atrophy that may have diagnostic significance, while serial MRI has an increasing role in the assessment of progressive atrophy (both generalized and regional) for diagnosis and prognosis. T2-weighted sequences are used to assess white matter signal change and tissue oedema. Additional sequences may be useful for certain indications, e.g. fluid attenuated inversion recovery (FLAIR) sequences to assess basal ganglia and thalamic signal in suspected prion disease, and diffusion-weighted imaging (DWI) to detect acute ischaemic damage which is probably the most sensitive imaging marker of prion disease with cortical diffusion signal change, reflecting spongiform histology.

Functional brain imaging techniques have a limited role in clinical practice. Metabolic imaging using single photon emission tomography (SPECT) or positron emission tomography (PET) may occasionally be useful in identifying regional functional changes in patients with frontal lobe syndromes and normal structural imaging; however, these techniques are not widely available and interpretation is difficult.

Electroencephalography

The EEG is generally of limited diagnostic usefulness in delirium, which is frequently accompanied by generalized slowing of cerebral rhythms indicating diffuse cortical dysfunction. As a tool for the detection of local pathology it has been largely supplanted by brain imaging techniques; however, it remains essential for the detection and localization of seizure discharges (particularly in non-convulsive status epilepticus). In dementia, the EEG is often helpful in the differential diagnosis. Conditions such as AD with diffuse cortical dysfunction are frequently accompanied by degeneration or loss of the normal alpha rhythm, while in focal dementias such as FTLD alpha rhythm is generally preserved at presentation. The EEG may also detect covert epileptiform changes in amnestic syndromes resulting from partial seizures, or periodic complexes in classic CJD, subacute sclerosing panencephalitis (SSPE) and other conditions with severe cortical derangement. Prolonged ambulatory or video-EEG may be indicated where there is strong suspicion of covert or unrecognized partial seizures.

Cerebrospinal fluid examination

Examination of the CSF is indicated where CNS infection is suspected, provided no contraindications exist (Chapter 8). Lumbar puncture is also recommended for younger patients with dementia and in cases where there is an unusual presentation or rapid course, to exclude an inflammatory process. Suspicious features include a raised CSF cell count (pleocytosis), and/or unmatched oligoclonal bands (indicating local synthesis of immunoglobulin in the CNS). Polymerase chain reaction (PCR) can be used to amplify and detect viral and other infectious agent DNA. Cytological examination may reveal atypical or malignant cells. Elevated total CSF protein is a non-specific finding in isolation. Elevated protein 14-3-3 is associated with rapid neuronal destruction in classic CJD, while elevated S-100 is associated with gliosis. However, despite much recent interest and good evidence that AD is associated with a reduction in CSF Aβ 1–42 and an increase in tau, diagnostically specific CSF protein biomarkers have yet to enter routine clinical practice.

Additional investigations

Additional investigations are dictated by clinical features in conjunction with the results of the initial battery (Tables 7.3 and 7.4). These may include vasculitic, infectious, autoimmune, neoplastic and toxicological investigations, and in younger patients, copper studies, white cell enzymes and genetic testing. HIV serology, although not routine, should always be considered, especially in younger patients or where risk factors exist. The more common familial dementias have autosomal dominant inheritance, and the diagnostic yield of genetic analysis is therefore likely to be higher in the younger patient with a positive family history (see Table 7.8); however, late onset cases of genetically mediated dementia do occur (e.g. in Huntington's disease) and the family history may be censored, incomplete or inaccurate.

Tissue biopsy may be required to establish the diagnosis in a minority of patients with dementia, especially in younger individuals, as directed by clinical features (Tables 7.2 and 7.8). Tonsillar biopsy has gained a place in the diagnosis of a small number of patients with suspected vCJD. Skin biopsy (including apocrine sweat glands) may detect abnormal accumulations in Lafora, Kufs or other storage diseases and in CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy). Nerve biopsy may be diagnostic in rare dementias with peripheral nerve involvement such as metachromatic leucodystrophy. Muscle biopsy including histochemistry and respiratory enzyme analysis may confirm a mitochondrial disorder. Marrow biopsy may identify the 'sea-blue histiocyte syndrome' of Niemann–Pick disease Type C and other storage diseases, and may also be indicated in the diagnosis of haematological and other malignancies in suspected paraneoplastic syndromes. Small bowel biopsy may be indicated to exclude Whipple's disease, and liver biopsy is occasionally indicated to exclude Wilson's disease. In exceptional cases, brain biopsy may be necessary where there is unresolved suspicion of a treatable (inflammatory or infectious) process where the diagnosis cannot be made by other means and potentially toxic treatment is contemplated. In some cases this is directed to a focal lesion; however, in most patients it is necessarily a 'blind' biopsy from the non-dominant frontal lobe. A full-thickness open biopsy including cortex, white matter and meninges should be performed by a neurosurgical team experienced in the technique. Disposable instruments should be used in cases where the risk of prion disease is considered clinically significant. Brain biopsy in patients with dementia carries an approximately 10% combined risk of significant morbidity or mortality, and should always be a carefully weighed decision.

The dementias

Alzheimer's disease

Alzheimer's disease (AD) is the most common cause of cognitive decline with AD pathology, in part or in whole, underlying at least 50% of all cases of dementia. AD is the prototypical cortical dementia against which other dementias are compared in a differential diagnosis. An understanding of the clinical features and diagnostic approach to AD is central to being able to distinguish the different dementias.

The prevalence of AD is strongly age-dependent – doubling every 5 years after the age of 60 years with around 1% of those aged 65–69 years affected rising to almost 20% in those aged 85 years or over. It is therefore important to have a low threshold of suspicion for cognitive decline in elderly patients who may not necessarily have cognitive problems as the presenting complaint; however, these impairments can complicate management of other neurological or medical conditions.

AD is also the most common cause of early onset dementia, arbitrarily defined as symptom onset before the age of 65 years. However, sporadic AD starting before the age of 50 years is very rare, and in these cases a genetic cause should, even in the absence of a family history, be suspected.

A definitive diagnosis of AD requires histopathological examination of brain tissue demonstrating excess accumulation of extracellular amyloid plaques and intracellular neurofibrillary tangles (Figure 7.2). The key building block (Chapter 2) of the amyloid plaque is beta-amyloid (Aβ), a 40–42 amino acid long peptide, formed following the cleavage of a much larger precursor polypeptide called amyloid precursor protein (APP) encoded by the APP gene on chromosome 21. Rare causes of autosomal dominantly inherited AD resulting from mutations in APP are caused by single peptide substitutions largely clustered around either end of the Aβ peptide – at sites of enzymatic cleavage from APP.

In established AD, amyloid plaques are found widely distributed throughout the cortex with heaviest deposition in the cortical association areas. Amyloid may also be laid down in cerebral blood vessels leading to amyloid angiopathy. The relative proportions of parenchymal amyloid (plaques) and vascular amyloid (angiopathy) varies considerably between patients. In familial AD and transgenic mouse models of AD, the relative proportions of these two forms of amyloid deposition seem to be related to the length of peptide generated by the pathogenic mutation, with a higher proportion of Aβ-42 promoting parenchymal deposition whereas relatively greater amounts of Aβ-40 leads to more vascular amyloid.

Neurofibrillary tangles result from the breakdown of the microtubule component of the neuronal cytoskeleton. Tau, a protein whose normal function is thought to be to promote and stabilize microtubule assembly, becomes hyperphosphorylated in

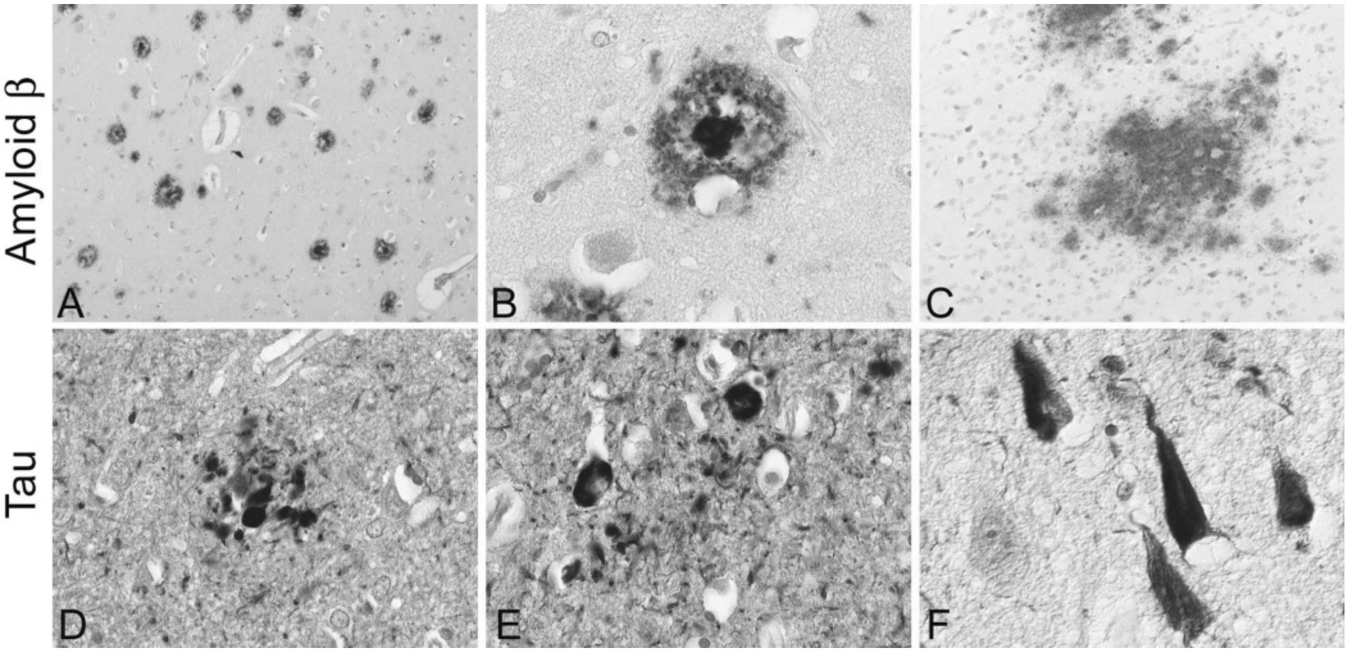

Figure 7.2 Alzheimer's disease: amyloid b (A, B, C) and tau deposits (D, RE, F): A, B: Autopsy specimen with abundant amyloid plaques in the neocortex seen at low power magnification (A), which are predominantly mature (neuritic) plaques which are characterised by a dense core and a peripheral halo seen at high power magnification (B). Diffuse plaques or large protein deposits (C) are probably a precursor of core plaques and can also be found in the ageing brain without being necessarily associated with dementia ('pathological ageing'). Neurites crossing the plaque become dystrophic and contain hyperphosphorylated tau protein, as shown in (D). Tau immunohistochemistry also shows multiple intraneuronal inclusions, so-called neurofibrillary tangles, which may assume various shapes (small globose perikaryal (E) band-shape, or flame shape (F), all at high power magnification.

AD and aggregates into an insoluble tangle within the neurone. Autopsy studies suggest that neurofibrillary tangles first appear in the entorhinal cortex before progressively involving the hippocampus and other limbic structures and then becoming widely distributed in neocortical association areas. Primary motor and sensory cortices are relatively spared.

Mutations in three genes are known to cause autosomal dominant AD with a high level of penetrance and usually with an early age at onset. Together these mutations account for only 1% of all cases of AD. Mutations in the *APP* gene, the first to be discovered, produce symptom onset typically between 45 and 60 years of age. Mutations in the Presenilin-1 gene (*PS-1*) on chromosome 14 account for approximately 50% of all autosomal dominant familial AD and often have the youngest age at onset: typically between 35 and 50 years of age but may be as early as 30 years and may occasionally present after the age of 65 years. Mutations in Presenilin-2 (*PS-2*) on chromosome 1 are relatively rare as causes of AD; cases have a young, although variable age at onset.

The clinical features of familial AD (whether resulting from *APP*, *PS-1* or *PS-2* mutations) are similar to each other and to sporadic AD (there are rare atypical presentations such as a spastic paraparesis in *PS-1*). Therefore, in a patient presenting with cognitive decline suggestive of AD with a family history of early onset dementia, testing for mutations in all three genes is appropriate. Presymptomatic testing of 'at-risk' individuals from known pedigrees is also possible, with appropriate counselling.

Overall, a family history of AD in a first degree relative occurring at any age confers an approximately twofold increase in an individual's lifetime risk. This is largely because of the risk-modifying effect of the apolipoprotein E gene (ApoE). ApoE exists in three isoforms: E2, E3 and E4. The most common isoform is E3, with E4 being less common and E2 relatively rare. Inheriting a single E4 allele increases the risk of AD approximately two- to threefold and is associated with an earlier age at onset. This risk is dose dependent, with homozygosity being associated with a four- to eightfold relative risk, and a mean age at onset 5–10 years earlier than average. However, the E4 allele is neither sufficient (in contrast to APP and presenilin) nor necessary to produce AD: approximately 20–30% of the general population carries one or more E4 alleles, and only 60–70% of all cases of AD have one or more E4 alleles. As a result, consensus guidelines do not recommend testing for ApoE as part of the diagnostic work-up of a patient with possible AD.

Clinical features and assessment

The regional distribution and progression of the pathology of AD largely accords with the march of clinical symptoms, which start insidiously, and gradually and inexorably progress. Obtaining a reliable history is key to the diagnosis. Patients often lack insight and it is essential to obtain a collateral history from a close informant. Partners or family members may not want to embarrass or contradict the patient and therefore, with the patient's consent, it is helpful to speak in part without the patient present in order to understand the extent of an individual's problems.

The most common complaint, often made by a carer, spouse or other family member rather than by the patient, is of problems with memory. Patients become repetitive in questioning, forgetting that they asked the same question recently, be it minutes, hours or days ago. Messages or errands are forgotten and there is progressive difficulty often with misplacing items (e.g. keys, glasses). A particular early feature of the memory deficit is the inability to place memories correctly; thus, patients may remember that someone visited but be unsure of the context (when the visit happened or who else was there). While many of these symptoms may be reported during normal ageing or by patients later determined to be 'worried well', what distinguishes AD is the severity of the deficit and its inevitably progressive nature.

In neuropsychological terms, these early symptoms reflect impairment of episodic memory. Recall is usually worse than recognition memory and although patients commonly lack insight into the severity of their problems they are often aware that memory is a problem. This memory deficit is a harbinger of the progressive impairment of all other higher cortical function. However, an isolated memory deficit is not sufficient for a clinical diagnosis of AD. Diagnostic criteria for AD require deficits in multiple cognitive domains of sufficient severity to impair activities of daily living. In the earliest stages, patients may have objective deficits of episodic memory without any other cognitive impairments and may have little problem continuing their activities of daily living. 'Amnestic Mild Cognitive Impairment' (MCI) describes such individuals with objective impairment of memory (scoring 1.5 standard deviations below the age-related mean for healthy controls) but without dementia. Longitudinal studies have shown that patients fulfilling criteria for MCI develop AD at a rate of about 10–15% per year. However, MCI represents a heterogeneous group and includes individuals who score badly on tests of memory because of anxiety or depression and also individuals who have static deficits, e.g. resulting from vascular damage.

How best to identify those patients who will go on to develop AD is a major topic of research. Some factors in the history may provide clues: if the carer is more aware of the problems than the patient, the probability of the symptoms being caused by AD is more likely. Conversely, if it is the patient who is complaining more of their problems than the informant, an alternative non-neurodegenerative cause is more likely. Asking the patient and informant to provide detailed examples of memory problems is often helpful. It is clearly less significant if someone occasionally forgets a message or cannot remember where they have placed an item when they have been distracted, multi-tasking or simply not been giving it their full attention. However, it is of more concern if the carer reports being asked frequently about the timing of hospital appointments or reports being cooked two evening meals.

There are a number of associated features that may accompany these early deficits. In particular, carers often report that the patient has become less confident, less spontaneous and more apathetic, and may seem depressed. Depression and AD commonly coexist and depressive symptomatology may mimic AD.

It is sensible to have a low threshold for suspecting and treating depression, ideally avoiding anticholinergic antidepressants. However, the presence and proportion of cognitive deficits are the key to determining that depression is related to the onset of AD rather than an alternative explanation. A common complaint of relatives of patients with AD is that initial problems were down to depression, and the cognitive decline overlooked because the informant's history was not properly considered.

As the pathological process progresses beyond the medial temporal lobes, so too do the cognitive deficits. Patients with AD typically develop cortical deficits that are symmetrical (left and right hemisphere involved simultaneously) and generalized (posterior cognitive functions affected as well as anterior). The clinical assessment therefore should aim to assess the pattern of cognitive decline from the history, from bedside testing and, ideally, with formal neuropsychometry. In addition to memory and orientation problems there are often subtle impairments of planning, decision-making and working out complex sequences, and learning new tasks (e.g. failures to master new equipment either at home or at work). Defining the presence of posterior (i.e. parietal and/or occipital) dysfunction should be sought, as this makes an alternative diagnosis of fronto-temporal dementia (FTD, see below) less likely.

Unlike fronto-temporal lobar degneneration (FTLD) syndromes and the frontal subcortical deficits of VaD, AD is not usually associated with marked behavioural and personality change in the early stages apart from a loss of confidence and some apathy. Thus, a useful contrast to FTLD is that spouses of those with AD usually feel that the patient has essentially the same personality. While problems with memory may be profound and individuals with AD are less confident in a number of cognitive areas, maintenance of a good social façade even in the presence of impaired insight, is a common feature of AD.

As the disease progresses, all these initially subtle cognitive deficits become marked and behavioural problems become more common. More severe language problems develop, including naming difficulties. Carers often report that patients no longer read as much as they have before, often because of a combination of impaired memory for what they have read and difficulties following the plot. With time, problems with speech and naming become increasingly marked, eventually leading to significant impairment of communication.

There may also be a history of increasing difficulty in using tools or implements which had previously not been a problem. Problems with praxis, which may sometimes be picked up in the early stages as subtle difficulty in copying complex hand movements, become more obvious with time.

Visuo-spatial difficulties may manifest as a deterioration in an individual's ability to drive, often reported by their passengers. Minor accidents may occur, as a consequence of misjudging distances or making incorrect decisions. This is compounded by a greater tendency to get lost in unfamiliar circumstances, and errors of judgement. Therefore, patients with a diagnosis of AD and their carers must be reminded of their legal obligation to inform licensing authorities (DVLA in the UK) and depending on severity may need to be advised to stop driving. In the later stages, agitation is relatively common and occasionally aggression often associated with frustration may be a major problem. Delusions are common and can be particularly distressing for patient and carer. The kernel of the delusions can often be understood in the context of failing memory and reasoning abilities, e.g. delusions of theft are common as an in-patient.

In the early stages, there are generally no focal neurological signs and apart from the praxis problems mentioned above, the examination may be normal. Myoclonus (often most noticeable in the fingers) may occur later in the disease, although patients with autosomal dominant AD tend to have early and prominent myoclonus, often a harbinger of seizures later on. In the late stages, there may be a generalised increase in tone in a *gegenhalten* fashion.

Brainstem and motor function are typically preserved when many higher cognitive abilities have been significantly degraded. Patients ultimately become unable to self-care but may still be capable of wandering, often with marked sleep–wake cycle reversal. In the later stages, problems with continence develop. Seizures, when present, are usually a late feature. Swallowing difficulties can also develop and contribute to pneumonia, one of the most common causes of death. Survival is age-related but is typically 5–15 years from first symptoms.

Investigations

Apart from familial cases where demonstration of a pathogenic mutation in *APP*, *PS-1* or *PS-2* is diagnostic, there are no definitive laboratory tests for AD. It is therefore important to exclude, as detailed elsewhere in this chapter, alternative causes for cognitive decline.

A number of investigations have positive predictive value for AD. Neuropsychometry is important in establishing the extent and pattern of cognitive deficits, and in established cases typically demonstrating deficits in a broad range of cognitive domains, prominent problems with episodic memory and posterior dysfunction at least as significant as anterior without a marked left–right asymmetry.

Current guidelines suggest that all patients with dementia should undergo structural imaging (CT or MRI) as part of their diagnostic work-up. As with neuropsychometry, structural imaging, in addition to excluding a space-occupying lesion, can help in making a diagnosis of AD by identifying the pattern of loss. AD is associated with marked and disproportionate medial temporal lobe atrophy, which is most easily assessed by looking for evidence of bilateral hippocampal atrophy (Figure 7.3). AD is also associated with ventricular enlargement and generalized cortical atrophy symmetrically involving both parietal and frontal lobes. These findings are best seen with MRI using a coronal T1-weighted volumetric sequence.

Imaging, and in particular MRI (T2-weighted or FLAIR), can be used to assess the extent of cerebrovascular disease. Functional imaging, PET and SPECT, show symmetrical temporo-parietal

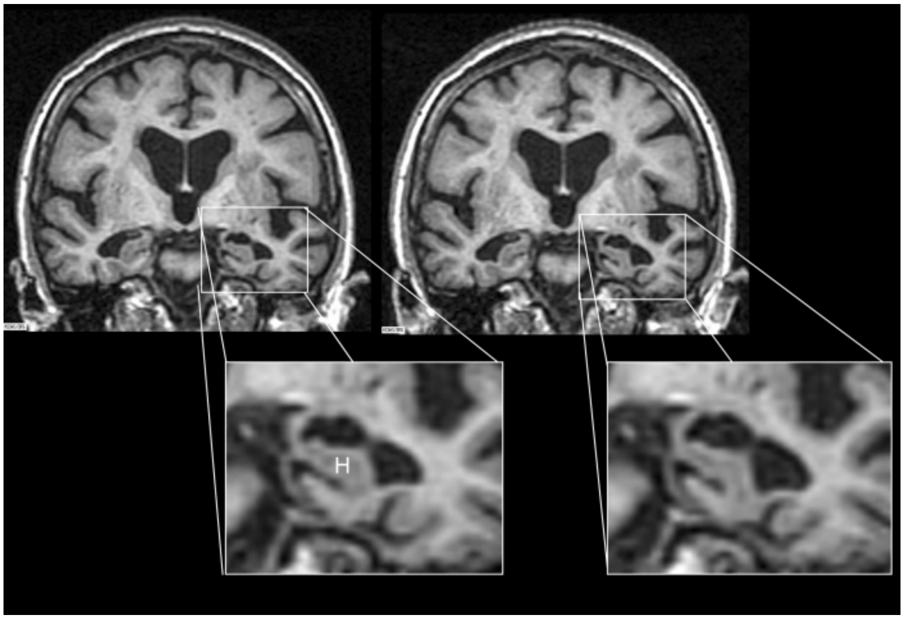

Figure 7.3 Hippocampal atrophy. Two coronal T1-weighted MRI scans of a patient with probable AD – baseline on the left; follow-up one year later registered to baseline. The inset shows a magnified view of the left hippocampus (H) with progressive atrophy over the year.

hypometabolism and hypoperfusion. None the less, the wide range of normality means either structural of functional scans may be reported as normal in the early stages of AD. Molecular imaging for AD (e.g. PET ligands for amyloid) appears very promising but are currently research tools.

EEG may be important to exclude seizure activity as a relatively uncommon cause of memory impairment and, if this is suspected, prolonged recordings may be required. In AD the EEG typically shows generalized slowing and loss of alpha rhythm, although in mild cases may appear normal.

There is increasing interest in using CSF markers to differentiate AD from other neurodegenerative dementias. In AD the CSF is usually acellular with normal protein. CSF tau (total levels and specific phosphorylated forms) are increased in AD while CSF Aβ-42 is reduced. The combination of these markers appears to differentiate AD from controls with sensitivity and specificity of approximately 90% but rather lower discriminatory ability to separate AD from other dementias.

Management

It is important that both patient and carer are considered in management. A holistic approach which covers social support, prognostic information and advice on legal, benefit and support issues is essential. Treatment of depression must be considered. Specific symptomatic pharmacological treatments for AD are discussed below; these include the cholinesterase inhibitors and memantine, an NMDA antagonist.

AD continues to be the subject of intensive research. Drugs aimed at modifying the disease process are under development. One promising strategy is Aβ immunotherapy which is currently undergoing stage III clinical trials. In mice such therapy has been shown to clear amyloid plaques from the brain and be neuroprotective if given before the onset of significant pathology. Other strategies include beta or gamma *APP* secretase inhibitors which aim to reduce Aβ production.

Cholinesterase inhibitors

The cholinesterase inhibitors (AChEIs) have been specifically developed as symptomatic treatment for AD. The rationale for their use is based on neurochemical findings in the cerebral cortex of patients with AD, in whom there is reduced activity of the enzyme choline acetyltransferase, with subsequent reduction in cortical levels of the neurotransmitter acetylcholine (ACh). By inhibiting the breakdown of ACh, AChEIs enhance the levels of ACh in cerebral cortex. There are currently three AChEIs licensed for the treatment of mild to moderate AD: donepezil (Aricept), galantamine (Reminyl) and rivastigmine (Exelon) (Table 7.5) Donepezil is a specific and reversible inhibitor of acetylcholinesterase (AChE), galantamine is a selective, competitive and reversible inhibitor of AChE, which additionally enhances the intrinsic action of ACh on nicotinic receptors, and rivastigmine inhibits both AChE and butyrylcholinesterase. They have similar efficacy; donepezil is available as a once-daily prescription and galantamine is available as a once daily slow-release preparation.

The clinical efficacy of AChEIs has been measured using the Alzheimer's Disease Assessment Scale (ADAS-Cog), which assesses cognitive function, and the Clinician Based Impression of Change

Table 7.5 Summary of NICE Guidelines for treatment of Alzheimer's disease (November 2006). See http://www.nice.org.uk/page.aspx?o=288826

NICE recommend donepezil, galantamine and rivastigmine as options in the management of moderate Alzheimer disease where MMSE is between 10 and 20 under the following conditions:

- Treatment should be initiated by specialists but may be continued by general practitioners using a shared care protocol
- The carer's views should be sought before and during treatment
- The patient should be assessed 2–4 months after a maintenance dose is established. Treatment should only continue if the MMSE has improved or not changed and if behavioural or functional assessment shows improvement
- The patient should be reviewed every 6 months. Treatment should usually only continue if MMSE score remains above 10 and it is considered that treatment is having a worthwhile effect on functioning and behaviour and the person's carer supports continued treatment
- It is recommended that therapy should be initiated with a drug with the lowest acquisition cost
- People with mild AD already on a cholinesterase inhibitor may continue on therapy until they or their carer consider it appropriate to stop

plus carer input (CIBIC-plus), which takes a more holistic view of the patient. A number of large randomized controlled trials have shown statistically significant, if clinically modest, symptomatic benefits of AChEIs on both ADAS-Cog effects and CIBIC over their 6-month duration, equivalent to a delay in symptomatic cognitive decline and temporary stabilization of the patient's clinical and functional state. Further, in open label extensions of these trials effects have been reported to last up to 5 years, and Cochrane reviews of donepezil and rivastigmine also report significant improvements on rating scales for activities of daily living and neuropsychiatric symptoms.

The use of AChEIs in dementia remains a hotly debated subject. There is disagreement over the quality and consistency of the clinical evidence, the size of benefits and the cost-effectiveness of treatment, where the cost of prescription is evaluated against the gain to the patient in terms of quality-adjusted life years (the CQG, or cost per quality year gained). The major criticism is the modest improvement afforded to most patients projected over several years, giving low CQG scores. Clinical experience and carer and patient analysis suggest that, while the response to treatment may be limited in the majority, up to 20% of patients have more dramatic improvements, which are concealed in averaged responses across the patient group. However, even small effects can significantly benefit quality of life for patients and carers. These are not easily costed and the financial calculations do not account for patients in whom treatment had been discontinued because of lack of response, nor for savings in carer input generated by treatment with AChEIs. In the UK, the NICE guidelines for the treatment of AD with AChEIs (November 2006) recommend their use only in patients with moderate AD (MMSE 10–20) (http://www.nice.org.uk). This recent recommendation to exclude patients with mild AD from treatment is based on an apparent lack of cost-effectiveness of treatment in this group. However, as mentioned above, this differs from anecdotal clinic experience. The value to affected individuals and their carers of some means of treating the progressive loss of intellect and personality to which they are condemned is also impossible to cost. The current NICE guidelines for treatment with AChEIs are summarized in Table 7.5.

The major problem in assessment of any individual is predicting who will respond to treatment, and to what extent. In general, when improvement occurs it appears to be maintained over several months, and while the extent of improvement may attenuate, the advantage over placebo can persist for several years. It is likely that use of AChEIs in combination with drugs acting on other neurotransmitter systems may work synergistically.

Treatment should be stopped when benefit is no longer evident. This is often a subjective decision made by the clinician after discussion with the patient and carer, based on either:

- A global impression; or
- Deterioration on a rating scale such as the MMSE.

As AChEIs can provide other benefits, particularly on behavioural and neuropsychiatric symptoms, their effectiveness in all areas should be considered. If in doubt, the drug should be withdrawn for a few weeks and if there is rapid decline in behaviour and/or cognition, the drug should be restarted. A trial of withdrawal should be considered on an annual basis.

Memantine

Memantine has an entirely different mode of action to the AChEIs, potentially preventing glutamate-mediated neurotoxicity. It is a voltage-dependent, moderate affinity, non-competitive *N*-methyl-D-aspartate (NMDA)-receptor antagonist and blocks the effects of pathologically elevated tonic levels of glutamate by preventing calcium influx into the neurone. It has beneficial effects in slowing cognitive decline in mild to moderate AD, but also in vascular dementia and is generally well tolerated. It was previously licensed for use in moderately severe AD. It is currently used when AChEIs are thought to have lost efficacy, in AD patients intolerant of AChEIs or in whom these are contraindicated (e.g. heart block). A recent randomized controlled trial showed that a combination of donepezil and memantine showed greater improvement in cognition, activities of daily living and neuropsychiatric symptoms than donepezil combined with placebo. Side effects are uncommon; they include hallucinations, confusion, dizziness, headaches and tiredness.

Fronto-temporal lobar degeneration

FTLD is an umbrella term that is used to describe the clinical features of a group of non-Alzheimer's neurodegenerative disorders. These fall broadly into three types, each of which is associated with a distinct set of presenting symptoms and distribution of regional cerebral atrophy involving frontal and temporal regions.

Frontal variant or fronto-temporal dementia

Frontal variant FTLD (fvFTLD) or fronto-temporal dementia (FTD) is the most common presentation of FTLD, accounting for over half of all cases seen. Patients typically present with personality change and breakdown in behaviour, including features such as apathy, sociopathy, disinhibition and euphoria. Invariably there is loss of insight and self-care early on, and later changes in food preference, hyper-religiosity, and stereotypic or repetitive behaviours.

Within fvFTLD, a distinction is recognized between patients who are disinhibited and socially inappropriate, and those who are apathetic. These two presentations are believed to reflect damage to dorsolateral and orbital regions of frontal cortex, respectively, although the prominence of individual symptoms may also depend on hemispheric involvement.

As the disease progresses, disruptive behavioural symptoms usually worsen. Disinhibited patients often develop inappropriate antisocial behaviours, and may even be arrested for stealing or disorderly behaviour. Angry outbursts are common, and conversation can be punctuated by tactless remarks. One-third of cases demonstrate emotional lability, changing quickly from inappropriate jocularity to passivity or anger. When apathy is dominant, patients become progressively inert, robotic and emotionally detached. Utilization behaviour, or environmental dependency, may be observed. For example, if the patient is offered a pair of spectacles then they will put them on; if offered another pair they will put them on over the first. Repetitive behaviours (checking, collecting, repetition of phrases or gestures) commonly develop. Such issues are often the most distressing for the family, and greatly increase the caregiver burden. Drug treatments or other mechanisms for dealing with these problems are unfortunately limited.

Neuropsychological testing may reveal executive impairment as the sole or most prominent finding, particularly within 2–3 years of disease onset. Other specific deficits (and the neuropsychological instruments with which they can be detected) include: a tendency to perseverate (verbal fluency), impaired planning (Wisconsin card sorting test), loss of inhibition, failure of recall with improvement on cueing (Wechsler Memory Scale), limited problem-solving (Raven's progressive matrices) and concreteness of thought (Cognitive Estimates test).

Imaging (MRI) may also be entirely normal in the early stages, revealing an asymmetrical pattern of atrophy of frontal and anterior temporal lobes as symptoms progress.

Temporal variant FTLD

The onset of temporal variant FTLD (tvFTLD), also known as semantic dementia (SD) is insidious, with a prodrome of 5 years or more often recognized retrospectively. Patients may complain of memory problems, but the presenting feature is typically word-finding difficulty, especially problems with producing people's names or common nouns. The earliest recognizable language deficit consists of fluent, and grammatically correct but empty spontaneous speech, with word-finding difficulties, circumlocution, impaired confrontation naming and reduced verbal fluency, especially for conceptual categories (e.g. types of animal or vehicle). Disintegration of general knowledge becomes apparent in failure of single word comprehension, and later of associative knowledge about concepts.

In contrast to the severe semantic deficit, phonology, prosody and grammar are relatively intact. Other aspects of language become affected to a degree, e.g. patients typically show a surface dyslexia such that irregularly spelt words (such as 'sew' or 'pint') are read according to typical spelling-sound mappings (in the example, to rhyme with 'few' and 'mint'). Later changes include loss of comprehension, echolalia (automatic repetition of words/phrases said to them) and bruxism. Other cognitive domains such as episodic memory, perceptual and visuo-spatial abilities are relatively preserved.

Imaging reveals severe asymmetrical anterior temporal lobe atrophy, in particular affecting the fusiform gyrus (Figure 7.4). Left temporal atrophy is dominant when the earliest symptom is one of verbal semantic loss, but when there is initial behavioural change, right temporal atrophy predominates. Left tvFTLD is three times as common as right tvFTLD, but both reflect similar pathophysiological processes (see below). It is unclear why the left temporal lobe should be more vulnerable to neurodegenerative pathology.

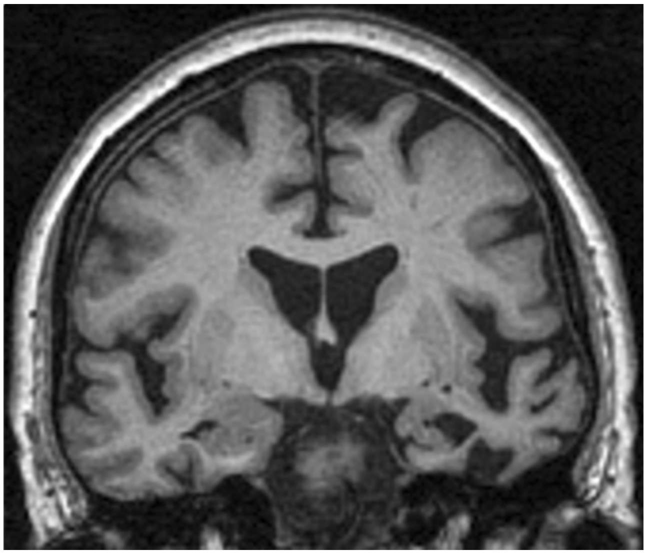

Figure 7.4 Coronal section of T1-weighted brain MRI showing focal atrophy predominantly involving the antero-inferior left temporal lobe, a pattern typical of semantic dementia.

Progressive non-fluent aphasia

The third common presentation is of a non-fluent language disorder, a deficit that usually remains circumscribed for many years, which may cause significant delay in presentation. Patients produce decreasing quantities of effortful, phonologically disrupted language, together with a strikingly preserved ability to understand individual words. Phrases become telegraphic, sentences short and disjointed, and comprehension is often impaired at the sentence level. Writing is similarly affected. Insight is usually retained, often with extreme distress.

In addition to the language-specific features there may be an associated orofacial apraxia, exacerbating the speech disturbance and sometime leading to difficulty swallowing. It is not until late in the course of the disease that behavioural features such as rigidity and loss of concern for others arise. This syndrome is associated with atrophic changes in the left inferior frontal and anterior insular cortex.

Neurological examination in FTLD is usually normal, although a subgroup of cases have or later develop additional signs of weakness and wasting in bulbar and/or limb muscles, in a pattern indistinguishable from amyotrophic lateral sclerosis (ALS). Primitive reflexes such as snout, suck and grasp may also become prominent in mid to late stages. Urinary and faecal incontinence occur in the final stages. Basal ganglia involvement can cause parkinsonism in some, and dysfunction of the frontal eye fields can cause abnormal saccadic eye movements.

Natural history

The three clinical subgroups progressively merge with time, such that in the later stages patients develop features of Klüver–Bucy syndrome: hyperorality may be demonstrated, with excessive gum chewing, smoking, drinking or eating. Most gain weight, although severely affected patients may place non-food items in their mouths. In addition, utilization behaviour (indiscriminate interaction with all items within reach) is often present.

In general, onset occurs between 50 and 65 years, with most patients surviving 6–12 years. Several studies have now suggested a faster rate of progression in FTLD (onset to death 6–8 years) than in AD (9–11 years).

Familial FTLD

Our understanding of the molecular genetics, biochemistry and neuropathology of FTLD is accelerating, thanks to recent advances in the genetics of familial FTLD. A large proportion of FTLD patients (35–50%) have a family history of dementia.

In tau-positive FTLD, microtubule associated protein tau (MAPT) mutations have been found to cause FTD and parkinsonism linked to chromosome 17 (FTDP-17), and have been linked to clinical syndromes resembling PSP, CBD and Pick's disease. Notably, considerable clinical heterogeneity is observed both between mutations and within families with the same mutation. Mutations in the progranulin gene also on chromosome 17 have been found to cause a large proportion of familial cases with tau negative ubiquitin positive inclusions (FTLD-U). Further, recent work has shed light on the nature of the protein components in FTLD-U. For example, TAR DNA-binding protein 43 (TDP-43) has been identified as a key protein in the ubiquitin inclusions of FTLD-U and in ALS, constituting a common pathologic substrate linking the two disorders.

Investigation

In the majority of cases the distinctive anatomical distribution of atrophy can be appreciated on structural or functional imaging. Although overlap at the clinical level inevitably occurs, advances in imaging have undoubtedly improved the accuracy with which the degenerative pathologies underpinning FTLD can be distinguished from that of AD during life.

EEG activity has traditionally been thought of as remaining normal in contrast to AD, in which absent alpha rhythm and generalized slowing are typical. A normal EEG in the context of progressive cognitive decline has therefore come to be regarded as supporting a diagnosis of FTLD. However, EEG abnormalities occur in over half of FTLD cases, and the severity correlates with disease progression in both FTLD and AD groups. The CSF is usually normal although cases associated with tau deposition may have raised CSF tau.

Neuropathology

Postmortem examination of the brains of patients with any of the FTLD syndromes can reveal shrunken cortical gyri, usually restricted to the frontal and/or anterior temporal lobes, reflecting underlying neuronal loss and gliosis. In some frontal cases, atrophy may be mild; the most common focus of frontal atrophy is the orbito-medial region, with additional involvement of the frontal pole, inferior frontal gyrus and insula. Disproportionate involvement of dorsolateral aspects may occur, but is less common. Temporal lobe involvement is typically concentrated in anteromedial regions, particularly the inferior and lateral surfaces, while the posterior two-thirds of the superior temporal gyrus are usually strikingly spared.

Three broad groups of histopathology can be distinguished:

1 Abnormal deposition of tau protein;

2 Inclusions negative for tau but positive for ubiquitin – a protein inclusion first described in association with the pathology of motor neurone disease (MND);

3 Neuronal loss and gliosis unaccompanied by any specific histological features.

Although there is still no universally agreed diagnostic terminology, most authorities refer to tau positive cases as Pick disease, and ubiquitin positive inclusion as fronto-temporal dementia with MND-type inclusions (FTD-MND) or ubiquitin positive FTLD-U and the non-specific cases as 'dementia lacking distinctive histology' (DLDH) (Plate 7.1).

Tau positive inclusions, which occur in around 20% of cases with the typical macroscopical pathology, are found in particularly high density in the hippocampal complex, and in layers II and VI of the frontal and temporal neocortex. A rather larger proportion have distended achromatic neurones, also immunologically positive for tau protein.

Ubiquitin positive inclusions typically appear in cortical motor neurones and the granule cells of the dentate gyrus. Although originally recognized as a histological characteristic of dementia in the context of MND, it is now known to be a common feature in cases without any neuromuscular involvement. Ubiquitin is a small (76 amino acid) protein forming part of a cytoplasmic system for the degradation and digestion of other intracellular proteins – a function critical not only for metabolic regulation, but also for cell signal transduction.

DLDH accounts for only a small number of cases, and may well dwindle further as new tools are added the pathologist's diagnostic armamentarium.

Although there is certainly no clear relationship between clinical and pathological phenotype, ubiquitin positive, tau negative inclusions appear to be a disproportionately common histological pattern among patients with SD. By contrast, tau positive pathologies occur most commonly in the context of the behavioural and PNFA variants.

Dementia with Lewy bodies and Parkinson's disease dementia

Dementia with Lewy bodies (DLB; also known as 'dementia associated with cortical Lewy bodies' or 'diffuse Lewy body disease') and dementia associated with Parkinson's disease (Parkinson's disease dementia [PDD]) together constitute the second or third most common cause of dementia in later life in most series. These disorders appear to lie on a pathogenetic and clinical continuum. Although estimates vary widely, dementia probably occurs in at least 20–40% of patients with idiopathic Parkinson's disease. Risk factors for development of PDD include increasing age, duration of disease and motor disability (especially symmetric, akinetic-dominant with speech and axial involvement), diminished response to levodopa and levodopa-induced confusion, early visual hallucinations and mood disturbance.

Pathologically, both DLB and PDD are characterized by the formation of Lewy bodies: intracytoplasmic eosinophilic neuronal inclusions with a central core and pale halo, containing the protein α-synuclein aggregated with abnormally phosphorylated neurofilaments and ubiquitin. Lewy bodies are found in the neocortex, limbic cortices and subcortical nuclei and there is associated neuronal loss. Pathological subtypes of DLB have been categorized as brainstem predominant, limbic (transitional) or diffuse neocortical based on the predominant distribution of pathological changes. No neuropathological features that reliably separate DLB, PDD and Parkinson's disease without dementia have been identified, and the particular clinical phenotype is likely to depend on the pattern of spread of pathological changes in the brain. In individuals developing DLB in later life, pathological features of AD (senile plaques and neurofibrillary tangles) commonly coexist at postmortem: this has given rise to the concept of a 'Lewy body variant of Alzheimer's disease' that is intermediate between Alzheimer's and idiopathic Parkinson's disease, and distinct from a pathologically 'pure' form of DLB that may occur in younger patients.

The pathological determinants of cognitive dysfunction in association with DLB and PDD are complex. Although it is not a universal finding, a number of studies have found a correlation between the regional density of cortical Lewy bodies and cognitive dysfunction (in particular visual hallucinations), while conversely, dementia is uncommon in patients with parkin mutations that lack cortical Lewy body involvement. Lewy bodies have also been correlated with cortical Alzheimer's changes, and it has been suggested that the interaction of these factors predisposes to the development of dementia and modifies the clinical phenotype. However, the development of dementia in some patients with synuclein mutations that lack significant associated Alzheimer pathology suggests that this is not a critical factor. Disruption of ascending dopaminergic and cholinergic pathways gives rise to clinically significant deficiencies of these neurotransmitter systems that interact with intrinsic cortical pathology.

Unresolved issues of pathological classification notwithstanding, DLB and PDD remain clinically defined syndromes and together these diseases present characteristic clinical problems that justify their status as a distinct dementia category. According to the current revised McKeith guidelines, DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism, and PDD when dementia develops in established Parkinson's disease. DLB is typically a sporadic disease of later life with an overall survival similar to AD; however, young adult, familial and rapidly progressive forms, although rare, are well-described.

Core features are progressive cognitive decline with fluctuating cognition, recurrent visual hallucinations and spontaneous parkinsonism. The cognitive profile is often dominated by executive, attentional and visuo-spatial disturbances. A history of some variation in cognitive function from day to day is common in many dementias; however, the fluctuations in DLB are more marked and often paroxysmal within a 24-hour period. They may manifest as drowsiness, decreased responsiveness or disorganization of speech or behaviour. Fluctuations may be profound and prolonged, and frank delirium with protracted confusion and hallucinosis may supervene. Visual hallucinations should be enquired about specifically: in DLB, they are generally animate, vivid, stereotyped and silent, and often emerge from background visual features or patterns under low-light conditions. Although it is a core diagnostic feature of DLB, parkinsonism is not recorded in a significant proportion of autopsy-proven cases, implying that the absence of extrapyramidal features does not exclude the diagnosis. Other characteristic features of DLB are marked neuroleptic sensitivity and REM sleep behaviour disorder, the occurrence of complex and bizarre (often violent) sleep-related behaviour because of acting of dream content (the result of abnormal restoration of muscle tone resulting from synuclein pathology in the region of the pontine tegmentum). Additional supportive features include recurrent syncope and falls, significant autonomic dysfunction, hallucinations in non-visual modalities, and early prominent delusions (including misidentification delusions such as the Capgras phenomenon and topographical and other reduplicative paramnesias), apathy and depression.

PDD has a very similar neuropsychological profile to DLB and shares many other clinical characteristics. Visual hallucinations are common in PDD even after medication effects are taken into account. In contrast to spontaneously occurring visual hallucinations, drug-induced hallucinations in treated Parkinson's disease are often perceived as frightening or threatening and accompanied by paranoid delusions. REM sleep behaviour disorder is also a feature of PDD. Parkinsonism in both PDD and DLB may closely mimic that of uncomplicated idiopathic Parkinson's disease, although predominant axial involvement with postural instability, absence of tremor and limited response to levodopa are more common.

Certain investigations in DLB and PDD can help to support the clinical impression, although no diagnostic or disease-specific biomarkers have been identified. On structural brain MRI, mesial temporal structures tend to be relatively better preserved than in AD. Metabolic brain imaging typically shows reduced striatal dopamine transporter uptake, and cortical perfusion and metabolism are globally reduced, often with a posterior emphasis. Degradation of alpha rhythm in the EEG occurs as a non-specific marker of cortical degeneration.

No specific or disease-modifying therapies are currently available for DLB or PDD. Cholinesterase inhibitors modestly improve cognitive function, attention, alertness and behaviour in a substantial proportion of patients, and indeed may be more effective than in AD at a comparable disease stage. More particularly, these agents may help in the management of fluctuations, sleep disturbance, confusion and hallucinations. The side effect profile of the cholinesterase inhibitors in DLB and PDD is broadly similar to that in AD. The impact on extrapyramidal symptoms is variable: modest benefit is seen in some patients, but significant worsening of parkinsonism or dystonia does occasionally occur and patients should be monitored for this possibility. The evidence base in favour of particular cholinesterase inhibitors remains limited and the choice of agent should be tailored to the individual patient (e.g. the convenience of once-daily dosing with donepezil set against the shorter half-life and more flexible regimen of rivastigmine). Neuroleptic drugs should in general be avoided in DLB and PDD, in view of the potential to cause severe, prolonged and sometimes life-threatening extrapyramidal reactions. However, these drugs may sometimes be necessary for the management of agitation or hallucinations where behavioural strategies or cholinesterase inhibitors have failed. In this situation, a new generation agent such as quetiapine or aripiprazole should be introduced cautiously and titrated slowly to the smallest effective dose. Management of parkinsonism in both DLB and PDD follows principles similar to those in idiopathic Parkinson's disease, although dopamine agonists are generally avoided because of their higher incidence of psychiatric side effects. Levodopa may benefit motor symptoms less than in uncomplicated Parkinson's disease, and dopaminergic effects on cognition are variable. Special care is needed to avoid exacerbating hallucinations and psychotic symptoms; in practice, the balance between immobility and confusion is often very finely poised and difficult to strike.

Dementia with other movement disorders

Cognitive decline is a feature of a number of other extrapyramidal disorders (described in more detail in Chapter 5), and most commonly manifests as a subcortical dementia resulting from involvement of fronto-subcortical circuitry. Although diagnosis generally rests on non-cognitive features, the type and relative prominence of cognitive deficits may assist in the clinical differentiation of atypical parkinsonism and 'Parkinson's-plus' syndromes. Progressive supranuclear palsy (Steele–Richardson–Olszewski syndrome) is frequently accompanied by profound bradyphrenia and executive deficits, which may include perseverative responses, environmental dependency and utilization behaviours. The 'applause sign' is characteristic: when asked to clap three times as fast as possible after the examiner, the patient makes additional handclaps or may initiate applause. In contrast to other 'Parkinson's-plus' disorders, cortico-basal degeneration is distinguished by early prominent cortical deficits such as limb and bucco-facial apraxia, parietal signs and impaired speech production, which may be relatively focal or asymmetric, and which overlap with disorders in the FTLD spectrum. It is also characterized by alien limb phenomena of variable complexity. Although severe cognitive decline is an exclusion criterion for multiple system atrophy, many patients do have mild executive deficits and cognitive slowing.

Cognitive impairment is a core feature of Huntington's disease. Attentional deficits and behavioural disturbances often dominate early in the disease course, and patients frequently present via psychiatric services, especially where the family history is concealed or not recognized. Visuo-spatial deficits are also well documented. Deficits of emotion recognition may be present, even in presymptomatic carriers. Cognitive decline in Huntington's disease has been shown to correlate with caudate atrophy and frontal hypometabolism, consistent with a primary disruption of fronto-subcortical circuitry.

Cognitive dysfunction is common in the expanding group of inherited spinocerebellar ataxias (Chapter 16), and executive and verbal memory deficits, affective disturbances and personality change have all been described. The severity of cognitive decline varies with the underlying genetic abnormality and may be particularly evident in *SCA2* and *SCA17*. There is much interest in defining a cognitive and behavioural signature of cerebellar damage, but this is difficult because of the frequent co-occurrence of damage involving other neuronal systems.

Prion disease

Introduction and disease biology

The prion diseases, or transmissible spongiform encephalopathies, are neurodegenerative conditions that affect both humans and animals. The human prion diseases have been traditionally classified into the Creutzfeld-Jakob diseases (CJD), Gerstmann–Sträussler–Scheinker (GSS) disease, fatal familial insomnia and kuru. Animal prion diseases include scrapie of sheep and goats, transmissible mink encephalopathy, chronic wasting disease of mule deer and elk, and bovine spongiform encephalopathy (BSE) which first appeared in the UK from the mid-1980s and rapidly evolved to a major epizootic estimated to have infected over two million UK cattle. BSE has since been reported from many countries. New animal prion diseases have since been identified, particularly of domestic and captive wild cats and ungulates. These diseases can be transmitted between mammalian species by inoculation or dietary exposure and the recognition of the novel human prion disease, variant CJD, from the mid-1990s onwards when experimental confirmation that it was caused by the same prion strain as BSE raised major public health concerns. While the number of human cases to date has been relatively modest, key uncertainties, notably with respect to major genetic effects on incubation period, allied with the widespread population exposure, suggest the need for caution.

Prions are transmissible agents with unique composition and properties, being apparently devoid of significant nucleic acid. Prion diseases are associated with the accumulation in the brain of an abnormal, partially protease-resistant, isoform of a host-encoded glycoprotein known as prion protein (PrP). The disease-related isoform, PrP^{Sc}, is derived from its normal cellular precursor, PrP^{C}, by a post-translational process that involves conformational change and aggregation. According to the 'protein-only' hypothesis, an abnormal PrP isoform is the principal, and possibly the sole, constituent of the transmissible agent or prion. PrP^{Sc} is hypothesized to act as a conformational template, promoting the conversion of PrP^{C} to further PrP^{Sc} by an autocatalytic process. In addition to public health concerns, prions have assumed much wider relevance in understanding neurodegenerative and other diseases involving accumulation of misfolded host proteins (protein-folding diseases).

Aetiological categories and classification of human prion disease

The human prion diseases are unique in having three distinct aetiologies (Table 7.6). They may occur sporadically, be acquired by dietary or iatrogenic exposure to prions, or inherited in an autosomal dominant fashion as a result of coding mutations in the prion protein gene (*PRNP*). Remarkably, Mendelian inherited forms of prion disease are also experimentally transmissible by inoculation of laboratory animals. The majority of recognized human prion disease occurs as sporadic CJD. The aetiology of

Table 7.6 Classification of human prion disease.

Aetiology	Phenotype	Frequency
Sporadic		
Unknown: random distribution worldwide; incidence of 1–2 per million per annum	Sporadic CJD: subacute myoclonic form and range of atypical forms; multiple distinct prion strains associated with distinct clinico-pathological phenotypes which includes sporadic fatal insomnia	~85%
Inherited		
Autosomal dominantly inherited conditions with high penetrance; all forms have germline *PRNP* coding mutations	Extremely variable: readily mimics familial Alzheimer's disease and other neurodegenerative conditions; over 30 mutations identified; includes Gerstmann–Sträussler–Scheinker disease, familial CJD and fatal familial insomnia	~10–15%
Acquired		
Iatrogenic infection with human prions via medical or surgical procedures: human cadaveric-derived pituitary hormones, tissue grafts and contaminated neurosurgical instruments	Iatrogenic CJD: typical CJD when direct CNS exposure; ataxic onset when peripheral infection	<5% (most from USA, UK, France and Japan)
Exposure to human prions via endocannibalism	Kuru	Unique to small area Papua New Guinea; major epidemic in 1950s with gradual decline since cessation of cannibalism
Environmental exposure (presumed dietary) to BSE prion strain	Variant CJD	Total to date ~200. Mainly in UK but now reported from a number of countries
Iatrogenic infection via blood transfusion from healthy donor infected with vCJD prions	Secondary vCJD	UK only to date

BSE, bovine spongiform encephalopathy; CJD, Creutzfeldt–Jakob disease; vCJD, variant CJD.

sporadic CJD is unclear but may arise from somatic mutation of *PRNP* or spontaneous conversion of PrP^{C} to PrP^{Sc} as a rare stochastic event. The alternative hypothesis, exposure to an environmental source of either human or animal prions, is not supported by epidemiological evidence.

Prion diseases show marked phenotypic variability. A major factor in explaining this diversity is the existence of distinct prion strains. Prion strains can be distinguished by differences in the biochemical properties of PrP^{Sc}. Prion strain diversity appears to be encoded by differences in PrP^{Sc} conformation and pattern of glycosylation. Four main types are seen amongst CJD cases, sporadic and iatrogenic CJD being of PrP^{Sc} types 1–3, while all variant CJD cases are associated with a distinctive PrP^{Sc} known as type 4 type (London classification). A similar type 4 PrP^{Sc} is seen in BSE and in BSE when transmitted to several other species. Such studies are allowing a molecular classification of human prion diseases although no internationally agreed classification has yet emerged and it is likely that additional PrP^{Sc} types or strains will be identified.

A common *PRNP* polymorphism at codon 129, where either methionine or valine can be encoded, is a key determinant of genetic susceptibility to acquired and sporadic prion diseases, the large majority of which occur in homozygous individuals. Heterozygosity is protective against developing sporadic and acquired prion disease and leads to increased age at onset in some forms of inherited prion disease. Codon 129 genotype also has a key role in determining clinicopathological phenotypes, in part via an effect on selection of particular prion strain types.

Sporadic prion disease

Creutzfeldt–Jakob disease

The core clinical syndrome of classic sporadic CJD is of a rapidly progressive multifocal dementia usually with myoclonus. The onset is usually in the 45–75 year age group with peak onset between 60 and 65 years. The clinical progression is typically over weeks progressing to akinetic mutism and death often in 2–3 months, most die in under 6 months. Prodromal features include fatigue, insomnia, depression, weight loss, headaches, general malaise and ill-defined pain sensations. Frequent additional neurological features include extrapyramidal signs, cerebellar ataxia, pyramidal signs and cortical blindness. About 10% of cases present initially with cerebellar ataxia.

Routine haematological and biochemical investigations are normal. There are no immunological markers and acute phase proteins are not elevated. Routine CSF examination is normal but 14-3-3 protein is usually elevated. However, it is also positive in recent cerebral infarction or haemorrhage and in viral encephalitis, and may also be elevated in rapidly progressive AD which may be difficult to clinically distinguish from CJD. CT or MRI is crucial to exclude other causes of subacute neurological illness but MRI has become increasingly useful in diagnosis of sporadic CJD, showing high signal in the striatum and/or cerebral cortex in FLAIR or DWimages (Figure 7.5). Cerebral and cerebellar atrophy may be present in longer duration cases. The EEG may show characteristic pseudoperiodic sharp wave activity which is very helpful in diagnosis but present only in around 70% of cases. Serial EEG is recommended to demonstrate this feature. Brain biopsy may be considered in highly selected cases to exclude treatable alternative diagnoses using appropriate CJD infection control precautions.

Neuropathological confirmation of CJD is by demonstration of spongiform change, neuronal loss and astrocytosis together with positive PrP immunohistochemistry. PrP amyloid plaques are usually not present in CJD. PrP^{Sc} can be demonstrated by immunoblotting of brain homogenates and is diagnostic of prion disease. PrP^{Sc} types 1–3 are demonstrated, distinct from type 4 which is exclusively seen in variant CJD. *PRNP* analysis is important to exclude pathogenic mutations even in the absence of a family history. Most cases of classic CJD are homozygous with respect to the common 129 polymorphism of PrP and MM is by far the most common genotype in classical subacute CJD.

Atypical forms of Creutzfeldt–Jakob disease

Atypical forms of Creutzfeldt–Jakob disease are well recognized. Around 10% of cases of CJD have a much more prolonged clinical course with a disease duration of over 2 years. *PRNP* codon 129 genotype is often VV or MV, rather than the MM type usually seen in subacute myoclonic CJD. Around 10% of CJD cases present with cerebellar ataxia rather than cognitive impairment, so-called ataxic CJD, although this presentation should lead to a consideration of acquired prion disease (see below). Heidenhain's variant of CJD refers to cases in which cortical blindness predominates with severe involvement of the occipital lobes. The panencephalopathic type of CJD refers to cases with extensive degeneration of the cerebral white matter in addition to spongiform vacuolation of the grey matter.

Acquired prion diseases

Kuru

Kuru is now largely of historical interest. It reached epidemic proportions amongst a defined population living in the Eastern Highlands of Papua New Guinea and was the major cause of death amongst adult women and children in the affected region when first described by Western medicine in the 1950s. It was the practice in these communities to engage in consumption of dead relatives as a mark of respect and mourning. Males over the age of 6–8 years participated little in mortuary feasts, which is thought to explain the differential age and sex incidence. It is thought that the epidemic related to a single sporadic CJD case occurring in the region some decades earlier. Its gradual disappearance since the cessation of cannibalism in the late 1950s has allowed estimation of the range of incubation periods possible in human prion infection which may exceed 50 years. The mean clinical duration of illness is 12 months with a range of 3 months to 3 years. The dominant clinical feature is progressive cerebellar ataxia. In contrast to CJD, dementia is much less marked.

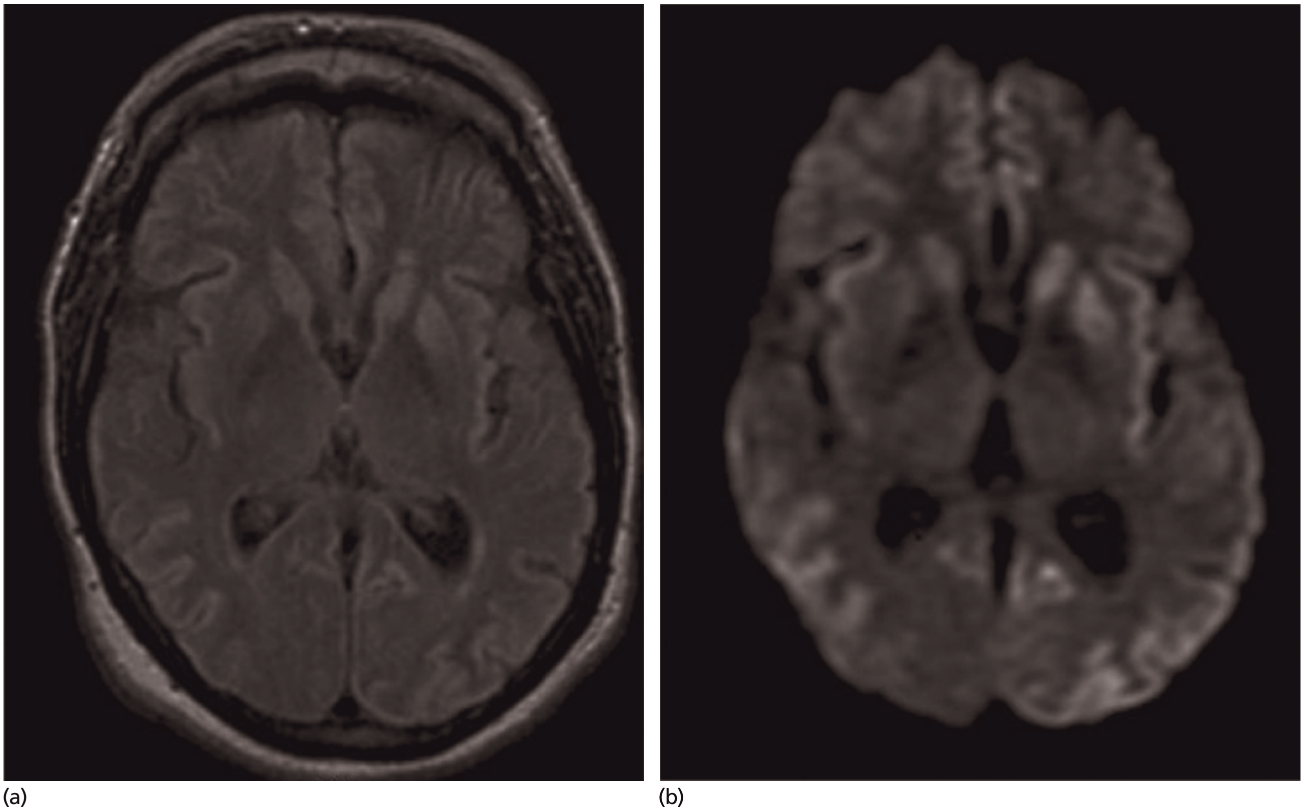

Figure 7.5 Sporadic CJD: MRI demonstrates typical increased signal intensity in the caudate and putamen bilaterally and widespread increased cortical signal intensity involving the occipital, frontal, temporal and insula cortex on FLAIR (a) and DWI sequences (b). The cortical signal changes are more apparent on the DWI images.

Iatrogenic Creutzfeldt–Jakob disease

Iatrogenic transmission of CJD has occurred by accidental inoculation with human prions as a result of medical procedures. Such iatrogenic routes include contaminated neurosurgical instruments, dura mater and corneal grafting, and human cadaveric pituitary-derived growth hormone or gonadotrophin. The diagnosis is usually based on a progressive cerebellar syndrome and behavioural disturbance or a classic CJD-like syndrome together with a history of iatrogenic exposure to human prions, and may occur in any age group. Cases arising from intracerebral or optic inoculation typically manifest clinically as classic CJD, with a rapidly progressive dementia, while those resulting from peripheral inoculation, most notably following pituitary-derived growth hormone exposure, typically present with a progressive cerebellar syndrome. The incubation period in intracerebral cases is short (2–4 years for dura mater grafts) compared with peripheral cases (typically 15 years or more). EEG, CSF and MRI are generally less diagnostically helpful than in sporadic CJD. *PRNP* analysis is important to exclude pathogenic mutations. Brain biopsy may be considered in highly selected cases to exclude treatable alternative diagnoses. Diagnosis is confirmed by PrP immunocytochemistry or Western blot of brain tissue for $\mathrm{PrP^{Sc}}$ types 1–3.

Variant CJD

This was first described in 1996. Its occurrence initially in teenagers and young adults and distinctive neuropathology differentiated it from sporadic CJD. A link with BSE was confirmed by molecular and biological strain typing of prions.

The early features of vCJD are non-specific, often with behavioural and psychiatric disturbances and in some cases with sensory disturbance. Initial referral has frequently been to a psychiatrist and the most prominent feature is depression but anxiety, social withdrawal and behavioural change is frequent. Suicidal ideation is infrequent and response to antidepressants poor. Delusions, which are complex and unsustained, are common. Other features include emotional lability, aggression, insomnia and auditory and visual hallucinations. A prominent early feature in some is dysaesthesiae or pain in the limbs or face which is persistent rather than intermittent and unrelated to anxiety levels. A minority of cases have been noted to have forgetfulness or mild gait ataxia from an early stage but in most cases overt neurological features are not apparent until some months into the clinical course. In most patients a progressive cerebellar syndrome develops with gait and limb ataxia. Cognitive impairment then occurs with inevitable progression to akinetic mutism. Myoclonus is seen in most patients, and chorea is often present which may be severe

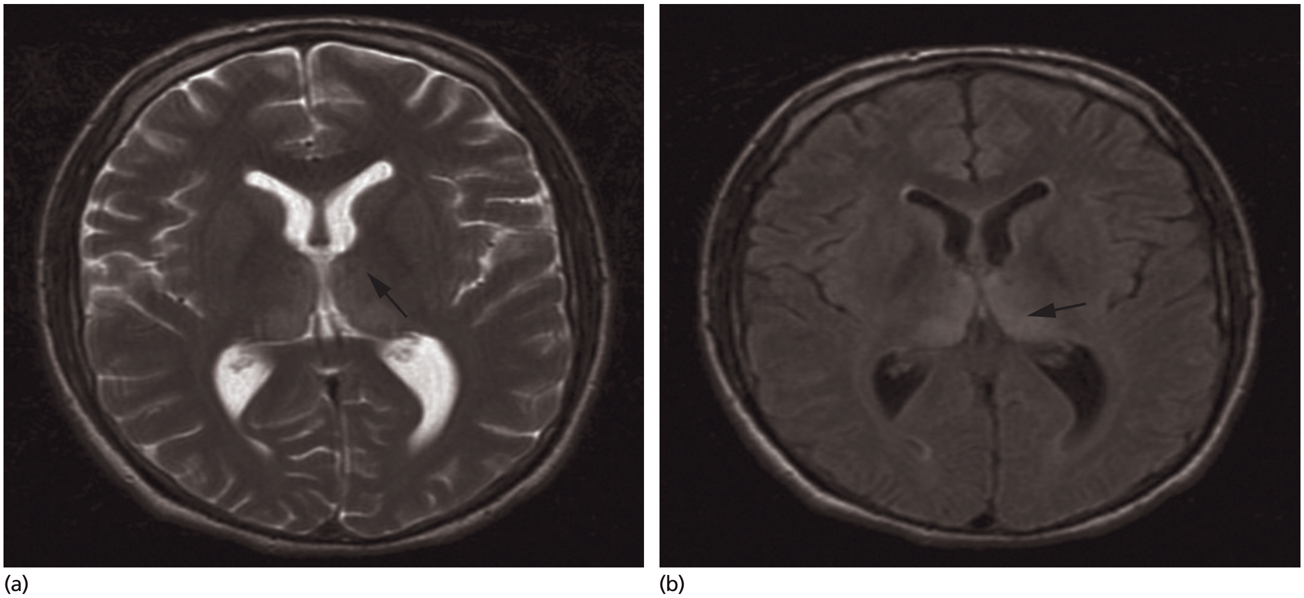

Figure 7.6 Variant CJD: MRI demonstrates symmetrical increased signal intensity in the pulvinar nuclei bilaterally (pulvinar sign) and dorsomedial thalami on T2 weighted (a) and FLAIR (b) sequences.

in some. Cortical blindness develops in a minority in the late stages of disease. Up-gaze paresis has been noted in some patients. Age at onset ranges from 12 to 74 (mean 28) years and the clinical course is relatively prolonged (median 14 months).

The EEG is abnormal, most frequently showing generalized slow wave activity, but without the pseudoperiodic pattern seen in most sporadic CJD cases. Neuroimaging by CT is either normal or shows only mild atrophy. The most useful non-invasive investigation is MRI, particularly the FLAIR sequence which demonstrates bilateral increased signal in the posterior thalamus (the pulvinar sign) in the large majority of cases (Figure 7.6). However, this sign appears as a late feature of the disease process and is not specific for vCJD; similar MRI appearances are described for example in sporadic CJD and paraneoplastic limbic encephalitis, both of which are important considerations in the differential diagnosis of patients with suspected vCJD. The absence of a pulvinar sign does not exclude a diagnosis of vCJD.

Tonsillar biopsy is a sensitive and specific diagnostic procedure for vCJD. Tonsillar $\mathrm{PrP^{Sc}}$ is uniformly present in clinically affected cases of vCJD but not in other forms of human prion disease. As infection of lympho-reticular tissues is thought to precede neuroinvasion, and indeed has been detected in archived surgical samples removed prior to development of vCJD, it is likely to allow firm diagnosis at the early clinical stage or indeed preclinically. A positive tonsil biopsy obviates the need for brain biopsy which may otherwise be considered in such a clinical context to exclude alternative, potentially treatable diagnoses. CSF 14-3-3 protein may be elevated or normal. *PRNP* analysis is essential to rule out pathogenic mutations, as the inherited prion diseases present in younger patients and may clinically mimic vCJD, and should be performed prior to tonsil biopsy. To date all clinical cases of vCJD have been of the *PRNP* codon 129 MM genotype. Whether vCJD will occur in other *PRNP* codon 129 genotypes at longer incubation periods remains to be seen and the VV and MV genotypes may result in a different disease phenotype which may involve propagation of distinct prion strains. Clinicians should therefore be alert to other manifestations of human BSE infection. Animal modelling using humanized transgenic mice also suggests that a sporadic CJD-like phenotype may result from BSE infection in the MM *PRNP* 129 genotype, raising the possibility that some cases of sporadic CJD may in fact be BSE related.

The neuropathological appearances of vCJD are striking and relatively consistent, generally allowing differentiation from other forms of prion disease. While there is widespread spongiform change, gliosis and neuronal loss, most severe in the basal ganglia and thalamus, the most remarkable feature is abundant PrP amyloid plaques in cerebral and cerebellar cortex. These consist of kuru-like, 'florid' (surrounded by spongiform vacuoles) and multicentric plaque types. Western blot analysis (molecular strain typing, see above) of brain tissue demonstrates $\mathrm{PrP^{Sc}}$ type 4 which is pathognomonic of vCJD.

Some of the features of vCJD are reminiscent of kuru, in which behavioural changes and progressive ataxia predominate. In addition, peripheral sensory disturbances are well recognized in the kuru prodrome. Kuru plaques are seen in around 70% of cases and are especially abundant in younger kuru cases. The observation that iatrogenic prion disease related to peripheral exposure to human prions has a more kuru-like than CJD-like clinical picture may well be relevant and would be consistent with a peripheral prion exposure.

Secondary (iatrogenic) vCJD

The prominent lymphoreticular involvement raised early concerns that vCJD may be transmissible by blood transfusion. Indeed, the tissue distribution is similar to that of ovine scrapie where prionaemia has been demonstrated experimentally. Since 2004, four transfusion-associated cases of vCJD prion infection have been recognized amongst a small cohort of now 23 surviving patients identified as having received blood from a donor who subsequently developed vCJD. The three clinical cases had the *PRNP* codon 129 MM genotype, while one patient, who died of an unrelated condition, was found to have prion infection at autopsy. This patient had the *PRNP* codon 129 MV genotype associated with relative resistance to prion disease. In each case transfusion was with a single unit of implicated red cells. The risk to recipients of blood from a silently infected donor appears very high. The incubation period in the clinical cases was 6–7 years. Clinical features and investigations are as for primary vCJD.

Inherited prion diseases

These are all adult onset autosomal dominantly inherited conditions associated with *PRNP* coding mutations (Figure 7.7). They were first classified as familial CJD and Gerstmann–Sträussler–Scheinker syndrome (GSS). Classic GSS is a chronic cerebellar ataxia with pyramidal features, with dementia occurring later in a much more prolonged clinical course than that seen in CJD. The onset of GSS is usually in either the third or fourth decades and characterized histologically by the presence of multicentric PrP-amyloid plaques. However, inherited prion disease kindreds show remarkable phenotypic variability, which can encompass both CJD-like and GSS-like cases as well as atypical cases which readily mimic other neurodegenerative conditions. Inherited prion diseases are a frequent cause of presenile dementia and a family history is not always apparent: *PRNP* should be analysed in all suspected cases of CJD, and certainly considered in all early onset dementia and in ataxias. Cases diagnosed by *PRNP* analysis have been reported that are not only clinically atypical, but also lack the classic histological features. Significant clinical overlap exists with familial Alzheimer's disease, fronto-temporal dementia, Huntington's disease, parkinsonian syndromes and ALS with dementia.

The identification of a pathogenic *PRNP* mutation allows not only molecular diagnosis of an inherited prion disease but also its subclassification according to mutation. Over 30 pathogenic mutations are reported in the human PrP gene and consist of two groups:

1 Point mutations within the coding sequence resulting in aminoacid substitutions in PrP or production of a stop codon resulting in expression of a truncated PrP; and

2 Insertions encoding additional integral copies of an octapeptide repeat present in a tandem array of five copies in the normal protein (octapeptide repeat insertion [OPRI]).

Notation for these diseases is 'Inherited prion disease (PrP mutation)', for instance:

- Inherited prion disease (PrP 6OPRI) or
- Inherited prion disease (PrP P102L).

The key clinical features in inherited prion disease are progressive dementia, cerebellar ataxia, pyramidal signs, chorea, myoclonus, extrapyramidal features, pseudobulbar signs, seizures and amyotrophic features, which are seen in variable combinations. The most frequent forms include PrP E200K, which may mimic subacute sporadic CJD (and in contrast to other inherited prion diseases often has a typical EEG), PrP P102L which may present as a progressive cerebellar ataxia or dementia, and insertional mutations which have a particularly variable clinical presentation, often with a long duration mimicking Alzheimer's disease. Fatal familial insomnia, usually associated with the D178N mutation, is characterized clinically by untreatable insomnia, dysautonomia and motor signs, and neuropathologically by

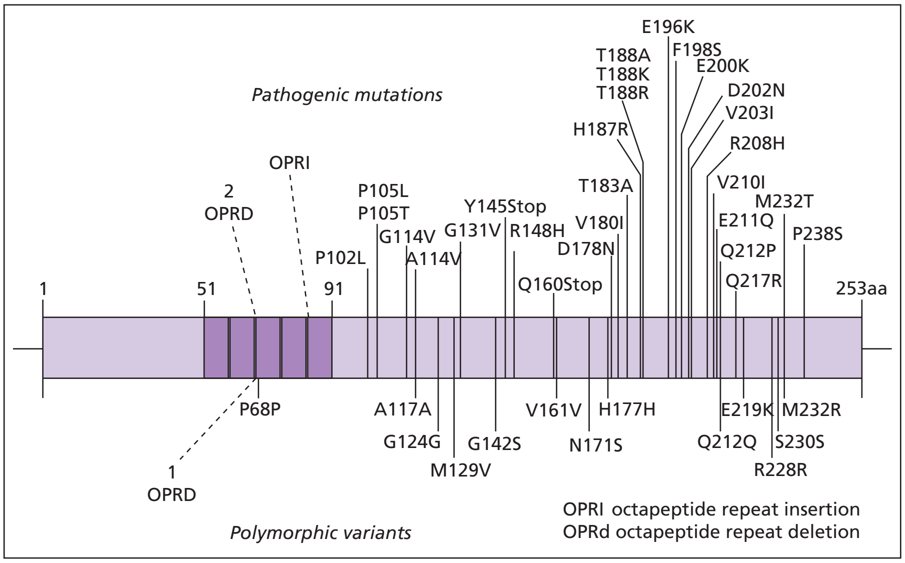

Figure 7.7 Pathogenic mutations and polymorphic variants in the prion protein gene.

selective atrophy of the anterior-ventral and mediodorsal thalamic nuclei. One variant, PrP P105L, presents as a progressive spastic paraparesis. Parkinsonism may be prominent in A117V and peripheral neuropathy occurs in E200K. Age at onset varies from the early twenties (seen often with insert mutations) to the seventies in some cases. The duration varies from less than a year to over 20 years.

Genetic counselling and presymptomatic testing

Direct gene testing allows unequivocal diagnosis in patients with inherited forms of the disease and presymptomatic testing of unaffected but at-risk family members, as well as antenatal testing. Most of the mutations appear to be fully penetrant; however, experience with some is extremely limited. Exceptions include E200K and D178N (fatal familial insomnia) where there are examples of elderly unaffected gene carriers. Genetic counselling is essential prior to presymptomatic testing and follows a protocol similar to that established for Huntington's disease. It is vital to advise both those testing positive for mutations and those untested but at-risk that they should not be blood or organ donors and that they should inform surgeons, including dentists, of their risk status prior to significant procedures, as precautions may be necessary to minimize risk of iatrogenic transmission.

Prevention and treatment

While prion diseases can be transmitted to experimental animals by inoculation, it is important to appreciate that they are not contagious in humans. Documented case-to-case spread has only occurred by cannibalism (kuru) or following accidental iatrogenic inoculation with prions. As discussed above, there is now evidence that vCJD prion infection is transmissible by blood transfusion. UK policy for some time has been to leucodeplete all whole blood and to source plasma for plasma products from outside the UK. A further possible route of transmission of vCJD is via contaminated surgical and medical instruments. Prions resist conventional sterilization methods and neurosurgical instruments are known to be able to act as a vector for prion transmission: several cases of iatrogenic transmission of sporadic CJD prions via neurosurgical instruments are documented. Recent epidemiological evidence suggests that classic CJD may also be transmitted by other surgical procedures. The wider tissue distribution of prions in vCJD together with the potential that significant numbers in the population may be silently infected has considerably increased these concerns. Effective products for prion-decontamination of surgical instruments are now available.

Certain occupational groups are at risk of exposure to human prions, e.g. neurosurgeons and other operating theatre staff, pathologists and morticians, histology technicians, as well as an increasing number of laboratory workers. Because of the prolonged incubation periods for prions following administration to sites other than the CNS, associated with clinically silent prion replication in the lympho-reticular tissue, treatments inhibiting prion replication in lymphoid organs may represent a viable strategy for rational secondary prophylaxis after accidental exposure. A short course of immunosuppression with high-dose oral corticosteroids in individuals with significant accidental exposure to human prions has been advocated.

Table 7.7 Prion diseases: useful websites.

UK National Prion Clinic, National Hospital for Neurology and Neurosurgery, London
http://www.nationalprionclinic.org

Medical Research Council Prion Unit, Institute of Neurology, London
http://www.prion.ucl.ac.uk/

UK CJD Surveillance Unit, Western General Hospital, Edinburgh
http://www.cjd.ed.ac.uk/

UK Department of Health
http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/CJD/fs/en

Human BSE Foundation
http://www.hbsef.org/

CJD Support Network
http://www.cjdsupport.net/

All patients with or at-risk of developing prion disease should be counselled on infection control as described above for gene carriers. New diagnoses should be notified to the local consultant in communicable disease control who can assess if public health measures are necessary, notably if a patient has had recent surgery or donated blood prior to diagnosis.

All recognized prion diseases are invariably fatal following a progressive course. A variety of drugs have been tried in individual or small numbers of patients over many years. There is no clear evidence of efficacy of any agent. Useful websites are summarized in Table 7.7.

Vascular dementia and vascular cognitive impairment

Cerebrovascular disease (Chapter 4) is a major cause of cognitive impairment and dementia both in its own right and in association with AD ('mixed dementia'). Dementia has been estimated to occur in up to one-third of individuals within a year of stroke. Despite its frequency and importance, there is little consensus as to how 'vascular dementia' should be defined, whether in clinical or research settings. 'Vascular cognitive impairment' (VCI) may be a more appropriate catch-all term, because it reflects the broad range of clinical presentations including (in addition to clearly progressive cognitive decline) static or indolent cognitive syndromes and mild cognitive impairment on a vascular basis. In contrast to AD and other primary neurodegenerative disorders, VCI has been relatively little studied. The status of 'mixed' dementia is a particularly vexed issue. The frequent coexistence of vascular and Alzheimer changes presents serious practical challenges to the development and interpretation of treatment trials in both diseases, as well as complicating the interpretation of epidemiological studies suggesting common factors that may predispose to both Alzheimer's disease and VCI.

Pathologically, there are no absolute criteria for a diagnosis of VCI. A spectrum of changes of variable severity occurs. Atheromatous involvement of large vessels may be found, although small vessel disease is typically prominent. Vascular changes are accompanied by lacunar and sometimes larger infarcts, typically in watershed regions between large arterial territories. Microscopically, there is lipohyalinosis of small arteries and arterioles, rarefaction and cavitation of white matter (leuco-araiosis) resulting from the conjunction of nerve fibre degeneration, gliosis and demyelination, and scattered cortical microinfarcts. Foci of old haemorrhage and amyloid angiopathy may also be observed. Pathophysiologically, whereas lacunes are the result of completed infarction, incomplete ischaemia resulting from partial vessel occlusion or hypotension can give rise to white matter lesions. There is evidence that autoregulatory perfusion reserve is decreased in zones of white matter damage, which is probably compounded by labile blood pressure control and raised plasma viscosity in vascular disease. The blood–brain barrier breaks down in these areas, and extravasated plasma proteins and other factors may contribute to neurotoxicity. Metabolic brain imaging and diffusion tensor MRI can demonstrate white matter abnormalities extending beyond the zone of damage on conventional structural brain imaging, underlining the dynamic nature of the vascular lesion and helping to explain why the relation between structural damage and cognitive impairment is not straightforward.

The clinical picture of VCI is diverse, and a given cognitive phenotype can result from a spectrum of pathogenetic mechanisms, including atherosclerosis, thromboembolism, thrombophilia, haemodynamic insufficiency, haemorrhage, and specific metabolic and genetic arteriopathies. Executive and attentional impairments, behavioural changes (disinhibition or abulia) and cognitive slowing with relative sparing of memory are clinical features common to many forms of vascular damage. This reflects the relative vulnerability of cognitive processes that depend on distributed neural networks and subcortical structures and pathways: an essential theme in our current understanding of VCI. Traditionally, emphasis was placed on the cognitive effects of acute stroke affecting a single large arterial territory or the stepwise accumulation of cognitive deficits accompanying recurrent cortical strokes: 'multi-infarct dementia'. However, it is increasingly recognized that VCI comprises a number of other clinico-anatomical syndromes, defined according to distinct patterns of clinical and brain imaging findings. Vascular changes are very common on brain imaging of healthy elderly individuals, and determining that a particular cognitively impaired individual has VCI, rather than an alternative cause such as AD, may be difficult. Diagnostic instruments such as the Hachinski Ischaemia Score are available but are of limited value in clinical practice.

Discrete strategically located cortical infarcts that implicate the medial frontal lobe (anterior cerebral artery) or mesial temporal lobe (posterior cerebral artery) can have a disproportionate effect on executive function and memory respectively: such lesions may simulate the cognitive effects of more diffuse brain damage. Single strategic subcortical infarcts can lead to impairment of multiple cognitive functions by damaging functional circuitry linking the cortex with subcortical structures or by interrupting projection pathways to the cortex. Critical sites include the thalamus, basal ganglia, internal capsule, limbic circuit and upper brainstem.

More commonly, VCI results from diffuse involvement of cerebral white matter and subcortical nuclei caused by small vessel disease. This is the clinical entity known as Binswanger disease, a somewhat controversial term that has also been applied to the neuropathological substrate. These patients typically present with an indolent cognitive decline and lack a history of clinical vascular episodes; the syndrome may closely mimic primary degenerative dementias such as AD. Clinical clues often include fluctuating deficits, bradyphrenia and prominent dysexecutive features. Memory impairment is frequent, although it is more variable, more dependent on attentional factors and more responsive to cueing than in AD. On neurological examination there may be brisk facial and limb reflexes and a short-stepped wide-based apraxic gait or marche à petit pas. Other features may include parkinsonism and other extrapyramidal syndromes, urinary incontinence or pseudobulbar palsy. A history of vascular risk factors (especially hypertension) should be sought but is of limited discriminating value. Patients undergoing major surgery (especially cardiac bypass) and those with congestive cardiac failure and orthostatic hypotension are especially vulnerable. However, an identical picture can occur even with a paucity of conventional vascular risk factors, suggesting that as yet undefined genetic and other factors also influence the development of cerebral small vessel disease.

The diagnosis rests on brain imaging findings of extensive, typical peri-ventricular white matter changes which spare subcortical U fibres and the corpus callosum and lacunes in the deep grey matter. MRI is the preferred modality because of its greater sensitivity; however, white matter changes may arise from a variety of different mechanisms and care is needed not to misclassify prominent peri-vascular spaces, which have no pathological significance. Existing brain imaging criteria for subcortical ischaemic vascular dementia have not been prospectively evaluated and do not reliably distinguish cases of 'mixed' dementia: although diffuse atrophy accompanies white matter damage, disproportionate atrophy of mesial temporal structures is a marker of AD. Although cognitive dysfunction (and more specifically, executive and attentional deficits) correlates with cerebral atrophy and with more severe white matter involvement, there is no agreement regarding the threshold, extent or distribution of the vascular lesion load required to produce cognitive impairment. Also uncertain is the relationship to the rate of accumulation of vascular lesions on serial imaging, although the rapid appearance of new lesions raises concern regarding an atypical aggressive process such as vasculitis or an active embolic source.

While MCI on a vascular basis is well-recognized clinically, consensus diagnostic criteria that could form the basis of large-scale observational studies or therapeutic trials have yet to be agreed. However, it is likely that conventional definitions of MCI that emphasize memory impairment will need to be modified to incorporate the early attentional and executive deficits that are clinical hallmarks of small vessel disease. Depression is an important consideration in such patients (as it is in all forms of VCI) because it is strongly associated with cerebral white matter disease and may amplify any cognitive deficit.

Although less common than ischaemic cerebrovascular disease, cerebral haemorrhage presents distinct diagnostic and management challenges, and multiple haemorrhages may simulate multi-infarct dementia. Hypertension is the key risk factor for most clinically significant cerebral haemorrhages; however, recurrent lobar haemorrhages are a marker for cerebral amyloid angiopathy. Pathologically, there is deposition of congophilic material (beta-amyloid peptide) in vessels of the cortex and leptomeninges, and there is a strong association with cerebral leuco-araiosis and cortical and subcortical microhaemorrhages. The origin of the vascular beta-amyloid is presently unclear. The extent of associated Alzheimer changes is variable, although these commonly coexist. Genetic factors influence the development of cerebral amyloid angiopathy: it is associated with ApoE epsilon-4 and epsilon-2, while the risk of cerebral haemorrhage is increased in association with the epsilon-2 allele. Rarely, cerebral amyoid angiopathy occurs on a familial basis with autosomal dominant inheritance, and various mutations leading to the deposition of specific amyloid proteins have been identified (Table 7.8).

A variety of other haematological, autoimmune, metabolic and genetic processes can cause VCI (Chapters 4 and 18). Clues to a process in one of these categories often lie in associated non-cognitive features, and they should be suspected in younger patients with a vascular phenotype but a paucity of conventional risk factors. The antiphospholipid antibody syndrome may produce dementia via ischaemic mechanisms and there may also be additional direct effects of the antibody on neural tissue. Cognitive impairment in sickle cell disease may reflect chronic hypoxia in addition to focal infarction. Of the genetic vasculopathies, CADASIL has attracted much interest recently as the culprit protein (a transmembrane receptor in smooth muscle cells coded by the *Notch3* gene on chromosome 19) appears to have a fundamental role in cell signalling, suggesting that this entity may be part of a broader spectrum of related disorders. Various presentations are possible, including psychiatric disturbance and acute encephalopathies, and a history of adult onset migraine is common. Brain MRI (T2 or FLAIR) characteristically shows involvement of white matter in the temporal pole and external capsule (Figure 7.8), unusual sites for conventional small vessel disease, and skin or muscle biopsy shows periodic acid–Schiff (PAS) staining of vessels and on electron microscopy granular osmophilic deposits adjacent to the basement membrane of arteriolar smooth muscle cells. The diagnosis is confirmed by screening the *Notch3* gene for known mutations; however, this is not straightforward as the gene is large and over 50 different mutations have been described.

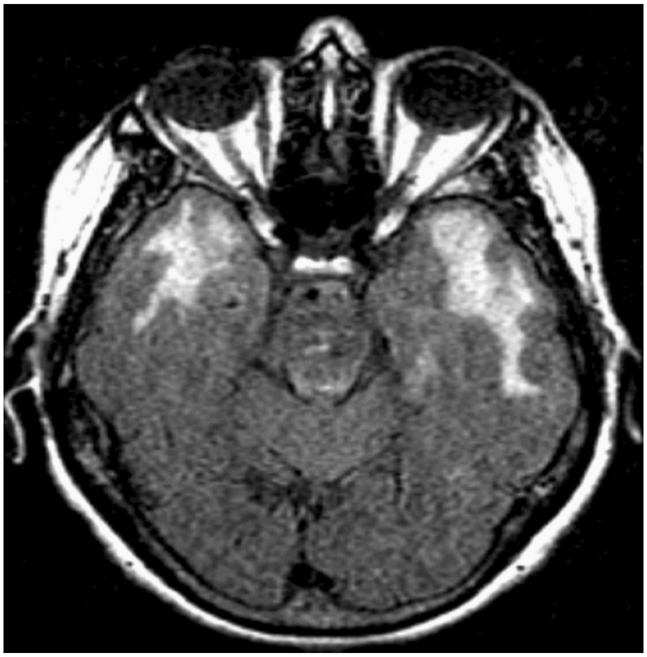

Figure 7.8 CADASIL. MR FLAIR axial image showing typical hyperintense white matter changes in each temporal pole. Courtesy of Queen Square Imaging Centre.

The differential diagnosis of VCI is potentially very extensive, because it overlaps with the spectrum of diseases causing subcortical dementia with cerebral white matter change. These include multiple sclerosis, progressive multifocal leucoencephalopathy, HIV dementia, lymphoma, post-irradiation, post-traumatic and post-hypoxic states, hereditary leucodystrophies and rare familial forms of AD with presenilin mutations. This list can usually be rationalized based on the clinical context. On imaging grounds, associated cortical infarction and involvement of the deep grey matter and brainstem are pointers to a primary vascular aetiology. Investigation of the patient with suspected VCI should include, in addition to the standard investigations listed in Table 7.4, an assessment of other end-organ damage (especially ischaemic heart disease) which may dictate overall prognosis. Brain imaging is essential and MRI is generally more informative than CT. Assessment of the carotid circulation is indicated where there is large-territory ischaemia or other suspicion of a symptomatic stenosis. Thrombophilia or other haematological or metabolic screens may be indicated, especially in younger patients. EEG often shows non-specific bitemporal slowing but preserved alpha rhythm, unless AD or another cortical degenerative process has supervened. CSF examination is indicated in younger patients or where an inflammatory or infective process is suspected and brain biopsy may be required in exceptional cases where cerebral vasculitis is likely.

The management of VCI rests on primary and secondary prevention of further vascular damage, based on principles similar to those that hold for cerebrovascular disease in general (Chapter

Table 7.8 A clinical classification of young onset and inherited dementias.

Family history	EPS	PYR	Atax	PN	Other features	Useful investigations	Gene	Diagnosis
a.d.	**Primary neurodegenerations**							
	–	+**	–	–	Myoclonus	MRI: symmetric hippocampal atrophy EEG: absent alpha	APP, PS1, PS2	Alzheimer's disease
	–	–	–	–	Epilepsy in neuroserpinopathy; inclusion body myopathy and Paget disease with valosin mutations Language output problems with progranulin mutation	MRI: fronto-temporal atrophy	ESCRT-III/Neuroserpin/ Valosin/Progranulin	Fronto-temporal dementia
	+	–	–	–	May have amyotrophy	MRI: asymmetric fronto-temporal atrophy	Tau exon10	FTDP-17
	+	–	–	–	Gaze apraxia	MRI: caudate atrophy	Huntingtin CAG repeat§§	Huntington's disease
	–	+	–	–	Dysfluency, fasciculations	MRI: asymmetric fronto-temporal atrophy		Motor neurone disease dementia
	+	–	+	–	Seizures		Atrophin1 CAG repeat	DRPLA
	+	+	+	+	Abn saccades	MRI: cerebellar atrophy	SCA1–17	Spinocerebellar ataxias
a.d.	**Prion diseases**							
	+	+	+	–	Florid myoclonus, cortical blindness, rapid course	MRI: signal change in basal ganglia EEG: periodic complexes in CJD	PRNP20: codon 178 (codon 129 val)	Creutzfeldt–Jakob disease
	+	+	+	–	Gaze palsy, pseudobulbar palsy, cortical blindness		Codon 102/others	Gerstmann–Sträussler–Scheinker
	+	+	+	–	Sleep disorder, dysautonomia		Codon 178 (codon 129 met)	Fatal familial insomnia
a.d.	**Vasculopathies**							
	–	–	–	–	Migraine, strokes	MRI: w.m. change anterior temporal lobe, external capsule Skin bx: osmophilic perivascular material	Notch3	CADASIL
	–	–	–	–	Strokes	MRI: lobar haemorrhages	APP, cystatin	Cerebral amyloid angiopathies
	–	+	+	–		MRI: w.m. changes	BRI	British dementia
a.d.	**Metabolic disorders**							
	–	–	–	+	Acute attacks, abdo pain, dysautonomia, seizures, *urine discoloration in light*	Urinary porphyrin screens		Porphyria* (acute intermittent)
	+	+	+	–	Palatal tremor	MRI: iron in basal ganglia Dec plasma ferritin	Ferritin light chain	Neuroferritinopathy

	Other disorders							
§	–	+	+	–	May have relapsing:remitting course	MRI: abn w.m. signal esp frontal, sparing U fibres	GFAP	Alexander's disease
X-L	–	–	–	+	Strokes, renal disease, *angiokeratoma corporis diffusum*, extremity pain	WBC enz: dec alpha-galactosidase		Fabry's disease*
	–	+	+	–	Episodes of vomiting, stupor, hyperammonaemia	Urinary organic acids		Ornithine transcarbamylase deficiency
	–	+	+	+	Adrenal insufficiency	MRI: diffuse w.m. change Inc plasma VLCFAs		Adreno-leucodystrophy
mat	+	+	+	+	Seizures, strokes, CPEO, myopathy, deafness, abn fundi, DM, LA, short stature	MRI: w.m. disease Muscle bx: may have ragged red fibres	mtDNA	Mitochondrial encephalopathies
a.r. (neg)	**Storage diseases**							
	+	–	+	–	Supranuclear vertical gaze palsy, seizures, organomegaly	Marrow bx: sea-blue histiocytes Fibroblast cultures: abn cholesterol esters		Niemann–Pick Type C
	+	–	+	–	PME, facial dyskinesias	Skin, muscle bx: inclusion bodies		Ceroid lipofuscinosis (Kufs)
	–	+	+	–	PME	Skin bx: Lafora bodies	Laforin	Lafora body disease
	–	+	+	–	Facial coarsening, *recurrent infections*, dysostosis, deafness, organomegaly	WBC enz: dec alpha-mannosidase		Alpha-mannosidosis
	–	+	+	–	PME, supranuclear horizontal gaze palsy, organomegaly	WBC enz: dec glucocerebrosidase Marrow bx: Gaucher cells		Gaucher's disease (subacute neuronopathic form)
	–	–	+	+	PME, visual loss with retinal cherry red spot, deafness, dysostosis	Inc urinary sialyloligosaccharides WBC enz: dec alpha-*N*-acetylneuraminidase		Sialidosis (mucolipidosis I)
	–	+	+	+	Optic atrophy	Fibroblast cultures: dec galactosylceramide beta-galactosidase		Globoid cell leucodystrophy (Krabbe)
	–	+	+	+	*Tendon xanthomas*, cataracts, diarrhoea, seizures	MRI: abn signal, esp cerebellar Inc cholestanol (bile acid intermediate) in serum, nervous tissue, tendons	Mitochondrial sterol 27-hydroxylase	Cerebrotendinous xanthomatosis*

Continued on p. 278

Table 7.8 *Continued*

Family history	EPS	PYR	Atax	PN	Other features	Useful investigations	Gene	Diagnosis
	+	+	+	+	Seizures	WBC enz: dec hexosaminidase A		GM2 gangliosidosis
	+	+	+	+		MRI: w.m. changes Urinary and peripheral nerve metachromatic deposits WBC enz: dec arylsulphatase-A		Metachromatic leucodystrophy
	+	+	+	+	Urinary incontinence	Skin bx: polyglucosan bodies	Glycogen brancher enzyme	Adult polyglucosan body disease
a.r.	**Other metabolic disorders**							
	+	–	+	–	*Corneal Kayser–Fleischer rings*, cirrhosis, haemolytic anaemia	MRI: *'face of the giant panda'* sign Dec serum copper and caeruloplasmin, inc urinary copper excretion		Wilson's disease*
	+	+	–	–	Seizures, visual loss	MRI: iron in globus pallidus (*'eye of the tiger'*)	PANK2	PKAN (Hallervorden–Spatz)
a.r.	**Other disorders**							
	+	+	–	–	*Bone cysts*, seizures, postural dyspraxia	MRI: basal ganglia calcification, inc w.m. signal	DAP12 TREM2	PLOSL: Nasu–Hakola disease
	–	+	+	–	Optic atrophy; may have onset with febrile illness or trauma	MRI: very extensive w.m. signal change	Eukaryotic initiation factor 2B	Vanishing white matter disease
Var								
	+	–	+	+	Orofacial dyskinesiae, seizures haemolysis in McLeod syndrome (X-L)	Acanthocytes on wet smears Inc serum CK Kell blood typing (McLeod)	VPS13A chorein/XK protein	Neuro-acanthocytosis

Pathognomonic features in italics.

* Specific treatment available.

§ Many cases represent new mutations.

§§ Mutations in SCA17 and Junctophilin-3 genes can cause a Huntington disease-like phenotype.

** Spastic paraparesis associated with some Presenilin 1 mutations.

abn, abnormal; a.d., autosomal dominant; APP, amyloid precursor protein; a.r., autosomal recessive; Atax, ataxia; bx, biopsy; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CK, creatinine kinase; CPEO, chronic progressive external ophthalmoplegia; dec, decreased; DM, diabetes mellitus; DRPLA, dentato-rubro-pallido-luyesian atrophy; enz, enzymes; EPS, extrapyramidal syndrome; esp, especially; FTD, fronto-temporal dementia; FTDP-17, frontotemporal dementia–parkinsonism linked to chromosome 17; GFAP, glial fibrillary acidic protein; HD, Huntington disease; inc, increased; LA, lactic acidosis; mat, maternal; neg, negative; PKAN, pantothenate-kinase-associated neurodegeneration; PLOSL, polycystic lipomembranous osteodysplasia with sclerosing leuco-encephalopathy; PME, progressive myoclonic epilepsy; PN, peripheral neuropathy; PS, presenilin; PYR, pyramidal signs; SCA, spinocerebellar ataxia; var, variable; VLCFAs, very long-chain fatty acids; WBC, white blood cell; w.m., white matter; X-L, X-linked.

4), and symptomatic treatment of cognitive deficits. Control of hypertension and other vascular risk factors is a core management priority to prevent recurrent stroke. Antihypertensive treatment should be introduced cautiously in light of the evidence for impaired autoregulation in patients with subcortical ischaemic damage together with antiplatelet therapy. The benefit of statins on VCI is not clear, probably reflecting the weaker part played by cholesterol in cerebrovascular disease. Randomized controlled trials suggests that the cholinesterase inhibitors are likely to be of symptomatic benefit in vascular dementia, although this is a difficult issue to resolve partly because of the problem of associated AD and also to the relative lack of suitable outcome measures (which tend to emphasize memory rather than the executive or attentional functions that are more relevant to VCI).

Dementia in young adults

Dementia is very rare before the fifth decade: in young adults and adolescents, inherited errors of metabolism and other genetic disorders are over-represented and many of these present as a 'dementia-plus' syndrome. The cognitive profile frequently takes the form of a subcortical dementia with prominent behavioural and affective features, or even frank psychosis, which may be misinterpreted as a pseudodementia. As cognitive impairment in young adult life is often constitutional or the result of congenital brain damage or static insults in early life, it is always important to establish whether cognitive dysfunction is progressive: this depends on a detailed history of pregnancy, birth and early milestones, and physical, social and scholastic development in later childhood. Cognitive decline often occurs in the setting of more widespread neurological and systemic disturbance and diagnosis generally depends on additional clinical and laboratory findings (Chapter 18).

Effective treatments with the potential for prevention or reversal of deficits are available for some inborn errors of metabolism, such as Wilson's disease (Chapter 5) and the porphyrias (Chapter 18). This large and diverse group of conditions also includes the mitochondrial cytopathies (Chapter 9) and a bewildering array of storage disorders (Chapter 18), in which the absence or partial inactivity of an affected enzyme leads to accumulation of abnormal material. The storage diseases can be subclassified in various ways: for example, according to the type of material deposited (e.g. glycolipid, glycosaminoglycan, lipopigment, cholesterol metabolites, polyglycosans), the primary site of cellular deposition (white matter in leukodystrophies, cell bodies in neuronal storage diseases), or the subcellular organelle affected (lysosomes, peroxisomes).

Clinicians may find it more useful to adopt a pragmatic approach based jointly on the availability of a family history and cardinal clinical features. This is the approach outlined in Tables 7.4 and 7.8. Many of these disorders have autosomal recessive inheritance, and family history is therefore often unrevealing; a history of parental consanguinity may therefore be crucial. Other diseases show variable inheritance (e.g. the mitochondrial diseases, as components of the respiratory chain are encoded both by nuclear DNA and maternally inherited mitochondrial DNA; Chapter 9). The presence of pyramidal, extrapyramidal, cerebellar or peripheral nerve signs are key diagnostic clues and help to direct investigations. Additional features such as seizures, retinopathy or deafness further restrict the differential diagnosis while certain features (such as corneal Kayser–Fleischer rings in Wilson's disease, or tendon xanthomas in cerebrotendinous xanthomatosis), if present, are pathognomonic of particular conditions.

Despite recent progress in elucidating the genetic and molecular basis of many inborn errors of metabolism, diagnosis remains challenging. This is compounded by the protean nature of the diseases themselves. Genetic diagnosis is not practical in many cases (e.g. Wilson's disease and Niemann–Pick disease), both because of the limited availability of the relevant tests and the intrinsic heterogeneity of the causative mutations. Specialized processing of tissue samples is often required (e.g. muscle for respiratory enzyme analysis in mitochondrial disease; axillary skin for storage bodies in Kufs or Lafora body disease; fibroblast cultures in Niemann–Pick disease; Table 7.8). Despite much recent interest in disease-modifying therapies such as enzyme replacement or bone marrow transplantation in certain diseases (e.g. Gaucher's disease), the availability of such therapies remains limited, and cognitive deficits are unfortunately generally refractory to their effects. Accurate diagnosis is nevertheless of paramount importance in this group both for prognosis and genetic counselling.

In addition to genetically based disorders, non-degenerative acquired causes of dementia are also relatively more common in younger patients. The importance of this group lies in the potential for reversibility in many infective, inflammatory and acquired metabolic conditions.

Reversible causes of dementia

Although they are individually rare, many causes of dementia are potentially reversible and this group includes many diverse disease processes. A syndrome-based approach to the diagnosis of reversible dementias is presented in Table 7.9. Patients presenting with these syndromes demand particular vigilance to ensure that a treatable process is not overlooked. Rapid clinical evolution is a feature common to a number of diseases in this category. However, it is important to emphasize that many cases of dementia resulting from a reversible process do not present with such clinical clues: all patients with dementia should therefore be screened for treatable contributions to their cognitive decline.

Neoplasms and other space-occupying lesions

A variety of intracranial space-occupying lesions may present with insidious cognitive or behavioural decline. Potential causes include tumours, infectious lesions, chronic subdural haematoma and hydrocephalus. Cognitive and behavioural presentations are particularly associated with lesions in the frontal lobes, corpus callosum and midbrain. There may be associated features such as papilloedema or focal neurological signs, seizures, or systemic

Table 7.9 Diagnosis of some reversible dementia syndromes.

Syndrome/clinical features§	Candidate diagnoses	Relevant investigations
Intracranial space-occupying lesions		
Insidious behavioural change, frontal-executive dysfunction, may have papilloedema, focal neurological signs, seizures	Intracranial tumour (primary, CNS lymphoma, metastasis), esp frontal lobe, corpus callosum, midbrain*	*CT/MRI*: focal or multifocal space-occupying lesions Biopsy or resection of lesion
Constitutional disturbance, fever, other systemic evidence of infection, immunosuppression (esp HIV)	Brain abscess, cysts, other infectious lesions	May have serological, CXR or other findings; may require biopsy or resection of lesion
History of head trauma (often absent), coagulopathy, altered alertness	Chronic subdural haematoma	*CT*: subdural haematoma (may be isodense depending on age; may be bilateral)
History of meningitis, subarachnoid haemorrhage; gait apraxia, urinary incontinence, subcortical dementia	Hydrocephalus (any cause)	*CT/MRI*: findings of hydrocephalus (disproportionate ventricular enlargement) ± causative lesion
CNS vasculitis (various syndromes may occur)		
Rapid course, headache, fluctuation	Primary angiitis of CNS CNS lymphoma, esp intravascular	*EEG*: slowing of rhythms (non-specific) *MRI*: ischaemic lesions, signal abnormalities *CSF*: >3 cells, OCBs Brain biopsy
Systemic features of autoimmune/connective tissue disease (esp lupus, polyarteritis, Wegener's granulomatosis)	Vasculitis associated with systemic disorders	Inflammatory markers, serological and other investigations, tissue diagnosis (e.g. skin, kidney, lung)
Fever, other evidence of chronic infection (e.g. varicella zoster)	Vasculitis associated with infection	*CSF*: positive PCR May require brain biopsy
Limbic encephalitis		
Memory and behavioural disturbances, fluctuating alertness, confusion, temporal lobe seizures	VGKC Ab syndrome	*MRI*: abnormal mesial temporal signal *EEG*: temporal lobe spikes *Serum*: hyponatraemia (non-specific); VGKC titre *CSF*: OCBs
May have peripheral neuropathy, ataxia, hypothalamic dysfunction, brainstem signs	Paraneoplastic syndrome*	*CSF*: pleocytosis, OCBs Antineuronal antibodies (anti-Hu, anti-Ma2), systemic screens for malignancy incl whole body PET, CT
May have systemic features of autoimmune/connective tissue disease	CNS vasculitis (isolated or associated with systemic disorders)	*CSF*: pleocytosis May require brain biopsy Systemic serological and other investigations, other tissue biopsy (e.g. skin, kidney, lung) if indicated
Acute onset, may have fever, immunosuppression	Infectious encephalitis	*CSF*: pleocytosis; HSV, HHV6/7 PCR
Epilepsy		
Discrete episodes, fluctuating course, patchy retrograde amnesia	Temporal lobe epilepsy – Transient epileptic amnesia	*EEG*: epileptiform discharges (esp temporal lobe) *MRI*: abn mesial temporal signal, hippocampal damage
Refractory seizures increasing in frequency (may be epilepsia partialis continua), lateralized signs	Rasmussen encephalitis*	*EEG*: lateralized epileptiform discharges *MRI*: progressive atrophy and abnormal signal involving one cerebral hemisphere
Extrapyramidal syndromes		
Tics – motor stereotypies, psychiatric disturbances, may have precipitating factor (e.g. respiratory infection)	ABGA syndrome	*MRI*: basal ganglia signal change *Serum*: ABGA titre
Encephalitis lethargica: sleep disturbance, psychiatric disturbances, ocular abnormalities, parkinsonism, dyskinesias; may have precipitating factor (e.g. upper respiratory tract infection)	Encephalitis lethargica* (?post-infectious)	*MRI*: basal ganglia, thalamic, midbrain signal change *CSF*: OCBs *Serum*: ABGA may be positive
Chronic meningitis		
Uveitis, hypothalamic dysfunction, cranial nerve signs or polyradiculopathy, systemic features; often recurrent episodes	Neurosarcoidosis	*CXR*: various patterns *MRI*: w.m. lesions ± meningeal enhancement *CSF*: lymphocytic meningitis
Oral and genital ulcers, uveitis, rash, posterior circulation strokes, racial predilection (especially Turkish/Japanese)	Behçet disease	*MRI*: brainstem, basal ganglia lesions *CSF*: lymphocytic meningitis

Table 7.9 *Continued*

Syndrome/clinical features§	Candidate diagnoses	Relevant investigations
May have evidence of primary tumour; headache, confusion, cranial nerve and radicular signs	Carcinomatous/lymphomatous/leukaemic	*CT/MRI*: may have mass lesions *CSF*: cytology, immunophenotyping (may need several)
Immunosuppression (incl HIV), systemic features, may have cranial nerve signs, strokes; travel, occupational exposures	TB/fungal/'atypical' infectious agents	*CXR*: frequently abnormal *CT/MRI*: meningeal enhancement, may have hydrocephalus, mass lesions (tuberculoma) *CSF*: lymphocytic meningitis, AFB and fungal cultures, cryptococcal Ag
Tick bite/travel to endemic area, skin lesion, arthritis, may have radiculopathies/mononeuropathies/encephalomyelitis	Lyme disease (neuroborreliosis)	*Serum*: Lyme serology (may be negative) *CSF*: pleocytosis (may be absent), Lyme serology
Argyll Robertson pupils (light-near dissociation), strokes, dorsal column signs (tabes dorsalis), HIV infection	Neurosyphilis	*Serum*: treponemal serology *CSF*: pleocytosis, treponemal serology
Infectious syndromes with posterior hemisphere signs		
Adolescent or young adult, history of measles, rapid course, florid myoclonus and seizures	SSPE*	*EEG*: periodic burst-suppression *CSF*: OCBs (measles-specific Ab)
Immunosuppression/haematological malignancies, often hemiparesis, ataxia	PML*	*MRI*: confluent posterior w.m. changes *CSF*: JC virus PCR
Other infectious syndromes		
HIV risk factors, AIDS-related illnesses, advanced immunosuppression, gait disorder, seizures	HIV (AIDS–dementia complex)	*MRI*: confluent w.m. changes *Serum*: HIV serology, low CD4 count
Arthralgia, gut symptoms, facial movement disorder (oculomasticatory myorrhythmia), supranuclear gaze palsy, myoclonus	Whipple's disease of CNS	*CSF*: Whipple PCR Duodenal biopsy
Acquired metabolic disturbances		
History of poor nutrition, food faddism, vegan, features of malabsorption; specific features (e.g. Wernicke–Korsakoff, pellagra)	Nutritional deficiency states	Dietary assessment, nutritional and malabsorption (incl coeliac) screens, empirical therapy (e.g. thiamine)
Clinical features of endocrine dysfunction	Endocrinopathies	
Clinical features of organ failure; organ transplantation	Uraemia Hepatic encephalopathy Pancreatic encephalopathy Cardio-respiratory failure	Biochemical and metabolic screens, organ-specific imaging findings
Obesity, morning headaches, daytime somnolence, snoring	Obstructive sleep apnoea	Sleep study
Toxicological exposures		
Alcohol dependence, may have cerebellar ataxia, peripheral neuropathy, features of Wernicke–Korsakoff encephalopathy	Alcoholic dementia*	Co-morbidities: nutritional screens, liver function tests, brain imaging (exclude SDH)
History of heroin inhalation ('chasing the dragon'), parkinsonism, ataxia, corticospinal signs, subacute encephalopathy	Pyrolysate encephalopathy	*MRI*: diffuse w.m. increased signal sparing U fibres (esp posteriorly)
Polypharmacy, recent changes in therapy, culprit agents	Iatrogenic	Medication review
Suspicion of overt or covert poisoning (e.g. occupational/environmental, recreational drugs, self-harm), specific systemic features; specific neurological syndromes may occur (e.g. vasculitis with cocaine, amphetamines)	Environmental poisons (e.g. carbon monoxide, heavy metals, solvents, herbicides), illicit drugs	Specific urine and blood screens if available, other specific findings (e.g. blood picture, EMG)

* Limited potential for reversibility.

§ Rapid course in many.

Ab, antibody; ABGA, antibasal ganglia syndrome; abn, abnormal; Ag, antigen; CXR, chest X-ray; esp, especially; HHV, human herpes virus; HSV, herpes simplex virus; incl, including; OCB, oligoclonal band; PCR, polymerase chain reaction; PML, progressive multifocal leuco-encephalopathy; SDH, subdural haematoma; SSPE, subacute sclerosing panencephalitis; VGKC, voltage-gated potassium channel antibodies; w.m., white matter.

evidence of infection or primary tumour; however, such clues are often lacking and the detection of a process that may be amenable to surgical intervention is the single most important justification for brain imaging in all patients presenting with dementia. Biopsy or resection of the lesion is usually required for a definitive pathological diagnosis.

There are a number of other mechanisms besides focal cerebral damage by which neoplasms may produce cognitive dysfunction: metabolic disturbances associated with systemic cancers, paraneoplastic syndromes and meningeal infiltration. Cerebral lymphoma is notoriously protean, especially the intravascular variant which can closely mimic cerebral vasculitis and requires brain biopsy for diagnosis. Antineoplastic therapies may also be implicated in both acute and chronic cognitive decline, including cytotoxic drugs (especially methotrexate, or where multiple agents have been used) and cranial irradiation; these different modalities interact and show a dosage effect, and their delayed effects may be difficult to distinguish from tumour recurrence. Leucoencephalopathy and cerebral atrophy may manifest as a late decline in cognitive function up to several years post therapy. Cranial radiotherapy also predisposes to accelerated cerebral atherosclerosis and secondary tumours.

Epilepsy and dementia

There are a number of mechanisms by which seizures can be associated with cognitive decline and dementia. Seizures themselves may cause cognitive decline, and it is particularly important to identify covert temporal lobe seizures that may cause an amnesic syndrome similar to degenerative dementias such as AD. The syndrome of transient epileptic amnesia is characterized by fluctuations in cognitive function associated with episodes of anterograde amnesia and retrograde amnesia incorporating time periods for which the patient has essentially no recollection. Exacerbation of deficits following sleep is characteristic. Other clinical features of temporal lobe seizures often coexist but these are variable and indeed pure ‘amnestic seizures’ may occur. Temporal lobe spikes may be evident in the surface EEG; however, a prolonged recording may be required. There may be evidence of hippocampal damage on MRI. Although the pathophysiology is not understood in detail, ictal hippocampal paresis with inability to transfer events into long-term storage is a plausible mechanism.

Cognitive dysfunction (in particular, impaired attention and bradyphrenia) may develop in association with a number of anticonvulsant agents, including phenytoin, topiramate and valproate (the last may also cause a hyperammonaemic encephalopathy). The potential for cognitive deficits following surgical resections for intractable epilepsy (chiefly, temporal lobectomy) has long been recognized and must be taken into account during surgical planning and pre-operative studies of the lateralization of cognitive functions (especially language and memory).

A number of disorders predispose to the development of both cognitive dysfunction and seizures: examples include intoxications and drug withdrawal (notably alcohol), intracranial infections, head trauma, stroke, intracranial space-occupying lesions, cerebral vasculitis and degenerative dementias including AD (generally, later in their course). In such disorders, care is needed to distinguish the cognitive effects of seizures from the underlying disease process. Complex partial seizures frequently accompany limbic encephalitis, whether infectious, paraneoplastic or autoimmune. Certain epilepsy syndromes are integral to primary disease processes that also produce progressive cognitive decline: these include epilepsia partialis continua in Rasmussen encephalitis and progressive myoclonic epilepsy in neuronal storage diseases associated with inborn errors of metabolism (Table 7.8).

Limbic encephalitis

Limbic encephalitis is a subacute encephalopathy characterized by short-term memory impairment, confusion, alteration of consciousness, complex partial temporal lobe seizures and psychiatric syndromes. Limbic encephalitis may be caused by a variety of conditions which include:

- Paraneoplastic limbic encephalitis.
- Autoimmune limbic encephalitis with VGKC antibodies:
- Peripheral nerve hyperexcitability (PNH) absent +/– tumour;
- Peripheral nerve hyperexcitability present (Cramp fasciculation syndrome, Isaac’s syndrome, Morvan’s syndrome).
- Steroid responsive encephalopathy:
- With antithyroid antibodies (Hashimoto’s encephalopathy);
- Without detectable antibodies.
- Inflammatory vasculopathy (CNS vasculitis, Susac’s syndrome, lupus cerebritis, Sjögren’s syndrome, antiphospholipid antibody).

Paraneoplastic limbic encephalitis (PLE) is associated with the subacute (>12 weeks) onset of antegrade memory impairment, temporal lobe seizures and psychiatric symptoms (particularly depression, aggressive psychosis, hallucination and personality change). There may be other associated constitutional symptoms resulting from the underlying cancer.

A number of tumours and associated antibodies are now recognized in this syndrome:

- *ANNA1 (anti-Hu)* bronchial small cell carcinoma;
- *Anti-Ma2 (anti-Ta)* testicular tumour;
- *CRMP5/(anti-CV2)* lymphoma, thymoma, bronchial small cell carcinoma;
- *ANNA3* bronchial small cell carcinoma; and
- *N type VGCC* bronchial small cell carcinoma, breast.

The primary tumours usually associated with PLE are small cell bronchial (50%), testicular (>20%) and breast (>13%). MRI shows non-enhancing increased signal in the mesial temporal lobes. The EEG shows diffuse slowing with epileptiform discharges and there is a CSF pleocytosis and elevated protein in >80%. Serum antineuronal antibodies are not detected in approximately 40% of cases of histologically proven PLE. The neurological presentation antedates the diagnosis of cancer in approximately 60% of cases and usually occurs in the absence of local or distant spread, emphasizing the importance of early diagnosis. Although extensive investigations for an underlying tumour may be necessary, whole body fluoro-deoxyglucose position emission tomography imaging (FDG-PET) is sensitive in detecting occult underlying tumours.

The mechanism of PLE is unclear but is probably related to cell-mediated immunity developing against cancer cells with the underlying antineuronal antibodies probably being markers rather than directly pathogenic. PLE may improve following removal of the primary tumour or with immunosuppression (usually steroids) but there is often a considerable residual cognitive impairment and seizures may persist.

Autoimmune limbic encephalitis associated with antibodies that react to neuronal voltage-gated potassium channels (anti-VGKC Ab) without neuromuscular hyperexcitability is indistinguishable from paraneoplastic limbic encephalitis with subacute cognitive impairment, behavioural change, confusion, disorientation and temporal lobe seizures which are difficult to control. MRI shows high T2 signal in the mesial temporal lobes. The condition is frequently associated with hyponatraemia. There may rarely be an underlying malignancy (small cell carcinoma or thymoma). In some patients the condition may be associated with REM sleep behaviour disorder or seizures. Some patients respond to corticosteroids, plasma exchange or intravenous human immunoglobulin suggesting the antibody may have a direct pathogenic role.

Neuromyotonia (Isaac's syndrome)

In this condition neuromuscular hyperexcitability occurs with the presence of anti-VGKC Ab, the condition is associated with myasthenia gravis and underlying neuroplasms including thymoma and squamous cell carcinoma. The acquired neuromyotonia is characterized by involuntary rippling of the muscles with twitching and stiffness, myokymia in which there are waves of muscle twitching. Cramp fasciculation syndrome is probably a mild variant of neuromyotonia without fibrillations.

Morvan's syndrome

In Morvan's syndrome there is associated CNS involvement with severe insomnia, seizures, hyperhidrosis and encephalopathy. Autonomic hyperactivity may occur with labile hypertension, tachycardia and increased salivation. It occurs more frequently in men (9 : 1). Typically, patients with Morvan's syndrome present with subacute encephalopathy including confusion, hallucination and fluctuating cognition. EMG shows spontaneous muscle fibre activity with fasciculation, myokymia and neuromyotonic discharges and there may also be a mild sensory neuropathy. The MRI is usually normal but the EEG may show considerable slowing although seizure discharges are not present. Morvan's syndrome is also associated with thymoma but may develop after thymectomy. There may be symptomatic improvement in both neuromyotonia and Morvan's syndrome with immuno-modulatory therapy (corticosteroids, azathioprine, cyclophosphamide, plasma exchange and intravenous immunoglobulin).

Steroid responsive encephalopathy with autoimmune thyroiditis (Hashimoto's encephalopathy)

This is associated with the presence of thyroid autoimmunity (serum microsomal, peroxidase or antithyroglobulin antibody) often without clinical or biochemical evidence of thyroid dysfunction. The significance of this association is uncertain as there is no obvious relationship between phenotype and type or titre of antibody (see below). Many patients may develop hypothyroidism later in the course of the disease. The condition is more frequent in women (4 : 1) and presentation may be highly variable with seizures, psychosis and stroke-like episodes. Occasionally, there may be tremor, myoclonus or sleep disturbance. Investigation characteristically shows an elevation of CSF protein and abnormal EEG. The MRI is usually normal but there may be subcortical white matter changes. The condition is responsive to corticosteroids but prolonged treatment may be necessary.

Infective, metabolic, toxic and other causes of dementia

Cognitive dysfunction is a frequent accompaniment of infective, metabolic and toxic disorders, whether systemic or restricted to the CNS. The primary disorders are dealt with at greater length in Chapters 8 and 18: here, basic principles relating to their effects on cognition are summarized. In the majority of cases, cognitive decline is acute and manifests as a delirium; however, in a smaller proportion an insidious deterioration ensues which may be difficult to distinguish from more common degenerative causes of dementia. The exact pathophysiology of cognitive decline is poorly understood in many cases and probably multifactorial. The cognitive profile itself is rarely diagnostic, and indeed remains poorly characterized for many of the disorders in this large and diverse group. Posterior hemisphere signs may be prominent in some conditions, such as progressive multifocal leuco-encephalopathy and subacute sclerosing panencephalitis. However, most diseases in this group can produce a variable combination of behavioural (including neuropsychiatric) and executive deficits, often with bradyphrenia: the pattern of a subcortical dementia. General clues that one may be dealing with a disease process in one of these categories include an aggressive course, evidence of active systemic disease and younger age. Risk factor profiles based on ethnic or geographical origin (many of these diseases are more common in poorer populations), occupational, travel or sexual habits, clinical infection or infectious contacts, immunosuppression or toxic exposures may raise suspicion of a particular cause. Characteristic and discriminating clinical features and investigations for some of these diseases are summarized in Table 7.3.

Controversial entities

A number of conditions often listed as causes of dementia continue to arouse controversy, because of uncertainty regarding the pathogenetic mechanism or the validity of the association with cognitive decline.

In addition to its well-recognized acute effects on cognition and behaviour, alcohol has an established association with dementia and forms a high proportion of young onset cases in community-based series. However, it is often unclear to what extent cognitive decline in an individual patient is attributable to the toxic effects of ethanol per se versus associated factors such as malnutrition (in particular, thiamine deficiency and Wernicke–Korsakoff syndrome), concomitant drug use, hepatic encephalopathy and other associated medical conditions, head trauma or the interaction of multiple factors. Marchiafava–Bignami disease, a rare degeneration of the corpus callosum, was described initially in male Italian red wine drinkers but is likely to be the result of an uncharacterized nutritional deficiency or osmotic demyelination. On balance, it is likely that chronic heavy alcohol intake can itself produce a dementia that includes frontal deficits and difficulty with complex learning and which is accompanied by generalized cerebral atrophy. Improvement in cognitive function may occur with prolonged abstinence, although little information is available concerning the time course or extent of this. A variety of neuropathological changes have been described in alcoholics, including cortical neuronal loss and gliosis, cerebellar degeneration, and atherosclerosis; however, none could be considered pathognomonic.

Head trauma is linked with ‘dementia pugilistica’, a syndrome of cognitive deterioration, behavioural change and parkinsonism of variable severity that is observed in boxers and other individuals who have sustained significant repeated head injuries. Pathologically, dementia pugilistica shares many features with AD, and indeed head injury is a risk factor for later development of AD in epidemiological studies. The level of risk is influenced by the severity and tempo of the injury (greater with loss of consciousness and with repeated insults) and possibly ApoE status (greater in those with the epsilon-4 allele).

The association between dementia and common autoimmune disorders such as Hashimoto’s thyroidopathy and coeliac disease is not straightforward. Such diseases may lead to cognitive deterioration secondary to a systemic disturbance such as hyperthyroidism or malabsorption. The key issue concerns the potential pathogenetic role of autoantibodies in causing cognitive decline in such disorders. Despite a growing literature on ‘Hashimoto encephalopathy’ its nosological status remains to be defined. This will require detailed clinico- and immuno-pathological correlation and ideally identification of an animal or other model in which the role of thyroid autoantibodies can be examined directly. In the absence of such confirmation, it is important to exclude other treatable processes (e.g. cerebral vasculitis) in all suspected cases of Hashimoto’s encephalopathy.

Normal pressure hydrocephalus (NPH) is considered here insofar as it has been overdiagnosed in patients presenting with cognitive impairment. It is traditionally listed as a cause of reversible dementia, heralded by a clinical triad of gait apraxia, urinary incontinence and cognitive decline. However, the validity of the term has been criticised. NPH appears to be an idiopathic communicating hydrocephalus in a high proportion of cases, although it may follow arachnoiditis, subarachnoid haemorrhage or head trauma. Impaired CSF resorption at the arachnoid granulations is most often proposed as the pathogenetic mechanism. Supportive radiological features include ventricular enlargement that is disproportionate to the degree of gyral atrophy, occluded cortical sulci, prominence of the third and fourth ventricles with no macroscopic evidence of ventricular obstruction, and (on MRI) an aqueductal CSF flow void. The demonstration of normal CSF pressure and clinical improvement following removal of a diagnostic aliquot of CSF are put forward as additional criteria for the diagnosis. This can be supplemented by prolonged monitoring to document phasic increases in CSF pressure, CSF conductance studies or cisternography. Although the potential for improvement following surgical insertion of a CSF shunt has often been emphasized, the relationship between NPH and cognitive decline remains unclear. ‘Pure’ NPH is uncommon. Many patients diagnosed with NPH have changes of small vessel disease and/or AD at postmortem, and it has been shown that patients with AD may improve transiently following ventricular drainage (the mechanism is not clear). Patients with ‘idiopathic’ NPH, long-standing symptoms, established dementia, or radiological evidence of significant cerebral atrophy or cerebrovascular disease generally fail to improve following CSF shunting. The shunt procedure itself carries a significant risk of complications such as subdural haematoma in this population.

Management of dementia

Risk factor management

The greatest risk factor for development of dementia is age. However, there are several modifiable risk factors. Moderate exercise and a modest, rather than excessive, intake of alcohol reduce the risk of dementia as does modification of vascular risk factors: obesity, hypercholesterolaemia, diabetes, hypertension and smoking.

Co-morbidity

Delirium is often a harbinger of dementia and patients with dementia have a lower threshold for developing delirium and will take longer to recover than those who are cognitively normal. The usual causes apply, such as infection (usually involving the urinary or respiratory tract), metabolic/biochemical derangement, hypoxic/ischaemic damage or medication. These should all be excluded as a cause and treated actively if identified.

Depression is both an important treatable cause and compounding feature of dementia, occurring in up to 20% of individuals with AD, vascular dementia and DLB. Over 50% of patients with dementia experience depressive symptoms at some stage. Symptoms should be actively sought and treated in any patient at presentation and during the course of their illness.

Older tricyclics should be avoided because of their anticholinergic effects. Selective serotonin re-uptake inhibitors (SSRIs) are also preferable in FTD, as they may be effective in modifying the behavioural symptoms, in addition to any depressive symptoms. As in all patients, side effects should be looked for and response monitored.

Epileptic seizures occur in patients with dementia at a higher prevalence than among healthy elderly individuals. The incidence of seizures among patients with dementia varies with the aetiology of the dementing illness. In patients with AD, approximately 10–22% have at least one seizure. Seizures usually occur several years post diagnosis, in moderate to severe AD. There is an increased incidence in early onset AD, especially with *PS-1* mutation. The incidence of seizures in other dementing diseases is less clear. Diagnosis can be delayed by difficulty in description as a result of cognitive impairment. The potential cognitive adverse effects of some antiepileptic drugs must be taken into consideration, and the lowest effective dosage should be used.

The majority of patients with dementia are cared for in the community, usually in nursing homes. Approximately 30% of patients in UK nursing homes are receiving antipsychotic drugs, usually neuroleptics. In dementia, particularly DLB, these drugs can have catastrophic consequences; atypical antipsychotics should be used in preference. Even these are not free of the risk of increasing side effects and confusion, therefore treatment titration must be cautious. It is also important to remember the reported increase in stroke risk with risperidone and olanzepine.

Behavioural management

Coping on a daily basis with challenging behaviour is a major burden for the carer of a patient with dementia. In the early stages, the major behavioural changes are seen in FTD, but other disorders may also produce significant behavioural problems at some stage. The loss of insight seen in some diseases, combined with the change in personality and disinhibition, have a huge impact on the carer, causing strain on the relationship and loss of sense of control. Another problem apparent in mild dementia is significant anxiety, which also may exacerbate behavioural problems.

In more severe dementia, a multidisciplinary assessment is required for behavioural modification. This approach tends to be most successful in patients in nursing homes. Behavioural modification may be achieved by altering the environment, if there is an external precipitant, or by conditioning techniques with positive reinforcement. Strategies may improve performance, e.g. scheduled toileting, or prompted voiding can reduce urinary incontinence. Playing music during meals and bathing can reduce disruptive behaviour. Exercise, massage and pet therapy have all been used to reduce abnormal behaviours.

Hallucinations often occur at home in dimly lit surroundings (so-called ‘sundowning’) and improved lighting may help; as always, intercurrent infections and drugs should be considered as possible exacerbating factors.

Patients may become irritable or angry at being disturbed at times of washing, dressing or eating. A considered response is needed, with maintenance of a respectful friendly approach, removal of exacerbating factors and consideration of behavioural measures such as distraction or ‘time out’.

Sleep cycle is often very disturbed – patients may be up all night and sleep all day. This can be extremely distressing for carers. It is important to exclude delirium, and to ensure structure and rewarding activities during the day. A routine should be established with a fixed bedtime, no stimulants and meal before sleep. If these fail, it is reasonable to provide a trial of medication, such as an anxiolytic.

Urinary and faecal incontinence may become a problem for multiple reasons: medical causes such as diabetes mellitus, or cortical loss of bladder control, reduced mobility; or cognitive causes such as poor recognition, disorientation or impaired planning. In addition to prompt treatment of medical problems such as urinary tract infections, simple physical measures can make a significant difference. Regular visits can reduce the likelihood of accidents; avoidance of bedtime drinks, labelling of the toilet to provide cues and the use of incontinence pads all help. Pharmacological therapies such as oxybutinin may help, but have the potential for worsening confusion and need to be monitored closely.

Safety

Patients with mild to moderate dementia usually function best in familiar surroundings. It is important to create an appropriate, safe and supportive environment to encourage optimal function. A home safety evaluation and appropriate modifications should be organized. For example, signs may be placed around the house to orientate patients.

Patients may become increasingly unstable on walking, yet be unaware of this because of their cognitive impairment. Wandering is a frequent problem, often associated with lack of stimulation and ensuing frustration. Behavioural measures such as increasing interaction, providing stimulation at day centres, encouraging exercise and increasing structure of the day may help. At times, locking doors is the only solution.

In patients with significant orobuccal apraxia, e.g. in progressive non-fluent aphasia, a feeding nasogastric tube, or even a percutaneous endoscopic gastrostomy, may be required. Patients and family may opt not to have this, but discussion is important. Broaching the subject early in the course of the illness, if swallow is involved, will enable the patient and carers to make an informed decision.

As dementia progresses, increasing supervision is necessary, eventually becoming continuous. This curtails the carer’s ability to continue working, and progressively reduces their independence. Day care centres can provide release for the carers during the week and give structure to the patient.

The issue of fitness to drive creates enormous anxiety for the patient diagnosed with dementia, who perceives removal of a licence as a loss of independence. Driving for patients with frontal impairment can be particularly difficult because of their lack of insight and poor judgement, and families often have difficulty in persuading patients to stop. In contrast, patients with AD often progressively curtail their driving activities as they realize they or their relatives feel unsafe. It is difficult to determine at what point an individual becomes sufficiently impaired to cease driving, and the relationship between the severity of dementia and driving abilities is complex. The UK driving licence law states that if at any time the licence holder becomes aware that he/she has a disability he/she must inform the driver and vehicle licensing authority (DVLA). The guidelines state that in general a patient able to attend to day-to-day needs, with adequate insight and judgement, and not disorientated in time or place may be fit to drive. A licence may be issued on a yearly basis with reassessment on each renewal. If in doubt, assessment at a mobility centre may be required; if serious doubt exists a medical adviser at the DVLA may require a test to be taken.

In practical terms, the issue must be discussed with the patient and family once a diagnosis of dementia is made. The patient should be reminded of their legal obligation to inform the DVLA. If the patient and family do not inform the DVLA, and the physician is concerned, then he/she can inform the DVLA directly. Each case is individual, and the discussion should include carers and the patient.

Caring for the carer

In the UK and USA, 33–60% of carers of patients with dementia are spouses, over 75% of whom are women. This profile, and the perception of the role of a carer, varies across cultures and socio-economic groups. In most of the Western world, where the extended family is small or may not exist, the burden of caring can be very high, often focusing almost entirely on a single, often elderly individual.

Dementia leads to dependency and often to problem behaviours, with resultant strains on the carer. Compared to age-matched non-carer controls, carers have problems in several areas:

- Depression, stress, low self-esteem and poorer sense of well-being are common and are more severe in young onset dementia and if the premorbid relationship was ambivalent.
- Carers experience poorer physical health, with higher levels of chronic conditions, more prescription and GP attendances and poorer self-perception of health.
- Social isolation is frequent as carers have less time for themselves for hobbies and going out, and may have difficulty coping with social embarrassment caused by the patient's behaviour.
- The cost of nursing, respite care and lost earnings should not be underestimated, and often has a huge impact on quality of life, compounding the above factors.

This complex relationship requires both formal support from professionals and informal support from friends and relatives. The carer's needs change through the evolution of the illness and often continue after the death of the patient. Local support groups and national associations are extremely important in this regard.

Planning for the future and end of life issues

If no will is in existence, this should be discussed amongst the family. In order to make a will the patient needs to understand what they are doing and the effect it will have: what they have to leave, and who might make claims on it. Advanced directives concerning treatment should also be considered when patients are competent.

In the later stages of dementia the individual becomes totally dependent in activities of daily living, needing continuous nursing care. Profound loss of memory may lead to inability to recognize familiar surroundings or family and friends. Almost all comprehensible speech may be lost. There are particular issues that emerge at this stage, many with ethical implications, including whether to place the patient in institutional care. Important issues in any setting include:

- *Feeding* Swallowing may be difficult and good nutrition becomes a priority. Individuals at this stage need speech therapist assessment of swallowing, dietitian advice on nutrition and consultation with family as to when and if to institute feeding devices.
- *Medical treatment* Weight loss and immobility contribute to vulnerability to pressure sores and infection. Issues of withholding life-prolonging curative treatment, including cardiorespiratory resuscitation need to be discussed with the family.
- *Postmortem diagnosis and brain donation* Clinical diagnostic accuracy in patients with dementia is at best 70–80%. Postmortem neuropathological examination can provide an accurate diagnosis with potentially important aetiological information for familial diseases. Families often gain benefit from contributing to research from tissue donation. Examination of the brain and use of tissue, however, can only be performed with written informed consent from the next of kin, even in the case of a coroner's post mortem.

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8

Infection in the Nervous System

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Infections involving the nervous system carry a high morbidity and mortality, particularly in developing countries where the burden of disease is great, diagnosis is difficult and limited resources mean that availability and access to treatment is poor. In the developed world, neurological infection is less frequent but continues to cause significant problems of diagnosis and management. Increasing global travel means unfamiliar organisms are encountered in unexpected settings; there is an increasing recognition that more familiar pathogens may manifest disease in varying patterns and settings and newer emergent pathogens have become important, particularly in the immunosuppressed patient.

Infections of the nervous system can be caused by viruses, bacteria, fungi or protozoa. They may affect the lining of the brain, CSF, brain parenchyma, spinal cord, nerve roots, peripheral nerve or muscle. Infections of the CNS may be divided into meningitis, encephalitis, focal suppuration or inflammation. In meningitis there is inflammation involving the pia and arachnoid mater and the subarachnoid space. Encephalitis is infection and inflammation within the brain parenchyma. Focal infection causes abscess formation within or immediately adjacent to the brain or spinal cord. These patterns may overlap and when infection involves the meninges, brain, spinal cord and nerve roots the descriptive compound terms are used: meningo-encephalitis, meningo-myelitis, encephalo-myelitis, meningo-radiculitis and meningo-encephalomyelitis. Neurological disturbances may also arise as a consequence of direct infection or from a secondary para-infectious immune-mediated mechanism.

The presentation of infections of the nervous system can be highly variable, ranging from acute fulminating meningitis or encephalitis leading to death within hours, to the development of disease many years after the initial infection. The spectrum of neurological manifestation is also highly variable, ranging from meningism and impaired consciousness, to signs of cortical and subcortical dysfunction, or involvement of the spinal cord, nerve roots, peripheral nerve or muscle.

Understanding of neurological infection has been advanced by new techniques of molecular diagnosis, in particular wider availability of polymerase chain reaction (PCR) assay to detect bacterial and viral nucleic acid in cerebrospinal fluid (CSF), and improved imaging of brain and spinal cord. There have also been many important recent advances in the development of new therapies targeted towards specific pathogens, such as antiretrovirus therapy, and in facing the challenges presented by increased antibiotic resistance of pathogens such as streptococcus, tuberculosis and malaria. Perhaps even more importantly, the global burden of infections of the nervous system has been greatly reduced by the development of effective strategies of prevention for conditions such as poliomyelitis, leprosy and malaria.

Bacterial meningitis

Bacterial meningitis is caused by a primary infection within the subarachnoid space that causes acute inflammation of the meninges (pia and arachnoid mater). It may be caused by a variety of organisms which vary in frequency according to the age of the host and other risk factors.

Epidemiology

The incidence of bacterial meningitis is 2–6/100,000 per annum with peaks in infancy, adolescence and the elderly. Common causes of bacterial meningitis by age and risk factors are shown in Table 8.1.

The incidence of *Haemophilus influenzae* type b and group C meningococcal (*Neisseria meningitidis*) meningitis has declined dramatically with the introduction of vaccination programmes.

Risk factors

A number of factors may contribute to the development of bacterial meningitis (Table 8.2).

Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

Table 8.1 Common causes of bacterial meningitis by age and risk factors.

Neonates (<3 months)	*Escherichia coli* Group B streptococcus *Listeria monocytogenes*
Infant and child (>3 months)	*Streptococcus pneumoniae* (pneumococcus) *Neisseria meningitidis* (meningococcus) *Haemophilus influenzae*
Adults <50 (healthy and immunocompetent)	*Streptococcus pneumoniae* *Neisseria meningitidis*
Adult >50	*Streptococcus pneumoniae* *Neisseria meningitidis* *Listeria monocytogenes*
Skull fracture/post neurosurgery	*Staphylococcus epidermidis, Staph. aureus* Gram-negatives (*Klebsiella, Proteus, Pseudomonas, E. coli, Serratia, Acinetobacter*) Group A and D streptococci *Streptococcus pneumoniae* *H. influenzae*
Shunt associated	*Staph. epidermidis, Staph. aureus* Gram-negative organisms Rarely, streptococci spp, diphtheroids, anaerobes
CSF leak	Gram-negative organisms *Streptococcus pneumoniae* (pneumococcus)
Pregnancy	*Listeria monocytogenes*
Immunosuppressed (e.g. malignancy, alcohol, diabetes mellitus, septicaemia, UTI)	*Listeria monocytogenes* Gram-negatives *Streptococcus pneumoniae* *Pseudomonas aeruginosa* Group B streptococcus *Staph. aureus* *Cryptococcus*
Rarer causes	*Salmonella, Shigella, Clostridium, Neisseria gonorrhoea*

CSF, cerebrospinal fluid; UTI, urinary tract infection.

Table 8.2 Risk factors for the development of meningitis.

Penetrating cranial trauma	
Foreign bodies within the CNS	CSF shunts predispose to staphylococcal meningitis
Defect in the immune system	Impairment of complement activation predisposing to the development of meningococcal meningitis Splenectomy or splenic dysfunction, as in sickle cell disease, associated with pneumococcal meningitis T lymphocyte dysfunction (HIV disease, chemotherapy or malignancy) predisposes to *Listeria monocytogenes* meningitis
Defect in the mucocutaneous barrier	Skull base fracture predisposes to pneumococcal meningitis

Pathogenesis

Bacterial infection reaches the CNS either by direct invasion, haematogenous spread or embolisation of infected thrombi. There can also be direct extension from contiguous structures via the diploic veins or erosion of an osteomyelitic focus. Also infection may be iatrogenic (e.g. following ventriculo-peritoneal shunt, intracranial pressure monitor or surgery).

In community-acquired meningitis the transmission of pathogenic bacteria occurs by respiratory droplets spread or close contact with a carrier. The process by which these bacteria gain access to the CNS is complex. Bacteria initially colonize the nasopharynx by attaching to epithelial cells using outer adhesive pili and membrane proteins. The risk of colonization of the respiratory epithelium is increased by damage caused by irritants such as a preceding viral illness or cigarette smoke. Their capsular polysaccharides help to overcome host defence mechanisms including impairment of mucosal immunoglobulin A (IgA). The bacteria are carried across the epithelial cell into the intravascular space where they are relatively protected from the complement-mediated humoral response because of their polysaccharide capsule.

Bacteria that survive in the bloodstream gain access to the CSF via the choroid plexus epithelium or cerebral capillaries. They cross between endothelial cells by disrupting intercellular tight junctions or causing endothelial cell injuries. Once the bacteria reach the CSF they are in an immunologically privileged site because of the relatively minimal complement-mediated humoral response. Bacteria multiply rapidly within the CSF and bacterial wall components released by lysis induce an inflammatory process involving the meninges and brain substance. This, in turn, leads to increased permeability of the blood–brain barrier allowing further leakage of plasma proteins into the CSF and this contributes to the inflammatory and purulent exudates within the subarachnoid space. There is initially a temporary increase in cerebral blood flow leading to disruption of cerebral autoregulation and an increase in intracranial pressure. Worsening exudates infiltrate the arterial walls leading to intimal thickening and large vessel constriction, eventually culminating in cerebral ischaemia. The development of systemic shock leads to a reduction in systemic arterial blood pressure and, because of the impairment in cerebral autoregulation, a consequent reduction in cerebral blood flow which exacerbates the cerebral ischaemia or infarction. There may also be a secondary thrombosis of the major venous sinuses and thrombophlebitis of the cortical cerebral veins. Finally, the purulent exudate can obstruct the resorption of CSF by the arachnoid villi or the flow through the ventricular system leading to obstructive or communicating hydrocephalus with interstitial cerebral oedema.

Clinical presentation

Meningitis is characterized by the presence of fever, headache and neck stiffness. There is usually associated nausea, vomiting, photophobia and progressive lethargy, stupor or coma, and epileptic activity may develop. Meningitis may evolve as a fulminating illness over a few hours, particularly in children, but progression is variable and less commonly can be a progressive subacute infection worsening over several days. Meningism is characterized by the presence of neck stiffness on passive flexion and Kernig's sign becomes positive if neck and back pain is felt when the patient is in a supine position and the hip and knee are flexed. Brudzinski's sign is positive when flexion of the neck results in spontaneous flexion of the hips and knees when the patient is in a supine position. Seizures may be focal or generalized and may occur either at presentation or at any time during the course of bacterial meningitis in up to 40% of patients. They may arise from focal arterial or venous infarction, haemorrhage, localized cerebral oedema or as a consequence of systemic features including pyrexia, septicaemic shock, toxicity or other metabolic derangement. Meningitis may lead to vascular occlusion and subsequent infarction of the brain or spinal cord, progressive cranial nerve lesions and hydrocephalus secondary to impaired CSF absorption and obstruction. Organ failure, hearing loss and limb infarction may also occur.

Investigation

Bacterial meningitis is accompanied by an elevated white cell count and raised inflammatory markers. In the presence of septicaemia, platelet consumption may occur with loss of clotting factors. There may be associated hypocalcaemia, hyponatraemia and impaired renal function with metabolic acidosis. Imaging should be undertaken urgently to exclude mass lesions, hydrocephalus or cerebral oedema which are a contraindication to

Table 8.3 Comparison of cerebrospinal fluid (CSF) findings in different forms of meningitis.

	Normal	Acute bacterial	Viral meningitis	TB meningitis	Fungal meningitis
Appearance	Clear colourless	Turbid	Clear/opalescent	Clear/opalescent	Clear
Pressure	Normal	Increased	Normal or increased	Increased	Normal or increased
Cells	0–5/mm^3	100–60,000/mm^3	5–1000/mm^3	5–1000/mm^3	20–500/mm^3
Polymorphs	None	>80%	<50%	<50%	<50%
Glucose	>3.5 mmol/L (75% blood glucose)	Low (<40% blood glucose)	Normal	Low <50% blood concentration	Low <80% blood concentration
Protein	<0.4 g/L	>0.9 g/L (1–5 g/L)	>0.4–0.9 g/L	>1 g (1–5 g/L)	>0.4 g (0.5–5 g/L)
Others		Gram-positive <90% Culture positive <80% Blood culture positive <60%	Culture positive <50% PCR	ZN stain positive <90% Culture positive 50–80%	Gram-negative Culture positive 25–50%

PCR, polymerase chain reaction; TB, tuberculosis; ZN, Ziehl–Neelsen.

Table 8.4 Treatment of bacterial meningitis.

Neisseria meningitidis (meningococcus)	Benzylpenicillin (penicillin G) 2.4 g (iv) 4 hourly for 7 days or Cefotaxime 2 g (i.v.) 4–6 hourly for 7 days or Ceftriaxone 2 g (i.v.) 12 hourly for 7 days or Chloramphenicol 50 mg/kg 6 hourly or Ampicillin 2 g (i.v.) 4 hourly for 7 days
Streptococcus pneumoniae	Cefotaxime 2 g (i.v.) 4–6 hourly for 14 days or Ceftriaxone 2 g (i.v.) 12 hourly for 14 days or Penicillin G < 2.4 g (i.v.) 4 hourly for 10–14 days
Streptococcus pneumoniae – moderate resistance	Cefotaxime 2 g (i.v.) 4–6 hourly for 14 days or Ceftriaxone 2 g (i.v.) 12 hourly for 14 days
Streptococcus pneumoniae – resistant	Cefotaxime 2 g (i.v.) 4–6 hourly for 14 days or Ceftriaxone 2 g (i.v.) 12 hourly for 14 days *and* Vancomycin 1 g (i.v.) 12 hourly for 14 days
Haemophilus influenzae	Cefotaxime 2 g (i.v.) 4–6 hourly for 14 days or Ceftriaxone 2 g (i.v.) 12 hourly for 14 days or Ampicillin 2 g (i.v.) 4 hourly for 14 days or Chloramphenicol 50 mg/kg 6 hourly
Streptococcus group A & D	Cefotaxime 2 g (i.v.) 4–6 hourly for 14 days or Ceftriaxone 2 g (i.v.) 12 hourly for 14 days or Penicillin *and* gentamicin 3–5 mg/kg/day in divided doses, 8 hourly
Listeria monocytogenes	Ampicillin 2 g (i.v.) (4 hourly) for 3 weeks *and* gentamicin
Staphylococcus aureus – non-MRSA	Flucloxacillin 2 g (i.v.) 6 hourly for 4 weeks
Staphylococcus aureus – MRSA	Vancomycin 1 g (i.v.) 12 hourly for 4 weeks
Gram negatives (excluding *Pseudomonas*) i.e. *E. Coli, Klebsiella* and *Proteus*	Ceftriaxone 2 g (i.v.) 12 hourly for 3–4 weeks or Cefotaxime 2 g (i.v.) 4–6 hourly for 3–4 weeks or Meropenem 2 g (i.v.) 4–6 hourly *and* vancomycin 1 g 12 hourly for 14 days
Pseudomonas	Ceftazidime 2 g (i.v.) 8 hourly for 3 weeks and gentamicin 3–5 mg/kg/day in divided doses, 8 hourly or Meropenem 2 g (i.v.) 8 hourly for 4 weeks

lumbar puncture. The diagnosis of meningitis is made by blood culture, CSF analysis, staining and culture. However, there is a considerable risk that lumbar puncture may cause coning in the presence of cerebral oedema. Therefore, in the absence of imaging, lumbar puncture should be avoided if the patient has impaired consciousness or there are focal neurological deficits, signs of shock or bleeding diathesis, purpuric or petechial rash, prolonged focal seizures or signs of raised intracranial pressure or incipient herniation.

Gram staining of the CSF is positive for meningococcus in approximately 50% of patients with acute meningococcal meningitis. Blood cultures may be helpful but are unreliable. CSF tests may directly identify an organism and its nucleic acid or surface constituents by staining, culture or capsular antigen detection. PCR is particularly sensitive in CSF for *Streptococcus pneumoniae* and *Neisseria meningitidis.* The CSF findings in different forms of meningitis are summarized in Table 8.3.

In patients with severe meningitis, the first priority is to commence empirical antibiotic treatment, usually immediately after sending a blood culture. Primary care physicians are recommended to commence benzylpenicillin in any child suspected of having meningococcal meningitis before transfer to hospital although the benefit of this approach is uncertain. If the situation is less urgent it is preferable to undertake a lumbar puncture, if safe, and send CSF for staining and culture before antibiotics are commenced. Empirical therapy in the absence of staining and culture depends on age, immune status and any other risk factors. In healthy immunocompetent adults treatment should be initiated with a third generation cephalosporin (not penicillin because of potential pneumococcal resistance) with ampicillin if *Listeria* infection is considered possible. When there is the possibility of nosocomial infection (e.g. following surgery, trauma or in the presence of a shunt) ceftazidine is preferred because it is more active against *Pseudomonas* than other third generation cephalosporins. Vancomycin is also added to cover highly resistant staphylococcus. If there is penicillin or cephalosporin allergy, chloramphenicol should be given with vancomycin. Specific antibiotic treatment for acute bacterial meningitis is summarized in Table 8.4 but therapy depends on demonstration of appropriate microbiological sensitivities.

Specific causes of bacterial meningitis

Neisseria meningitidis (meningococcal meningitis)

This is a Gram-negative diplococcus. It is the most common identified cause of meningitis in children and young adults, with an incidence of 1–1.5/100,000. In the UK, meningococcal disease remains the leading infectious cause of death in childhood with a mortality of approximately 10%. It occurs throughout the year but the majority of cases are in the winter and early spring. Transmission occurs by droplet spread, particularly in close contact, and 5–10% of all adults are asymptomatic nasopharyngeal carriers of these pathogenic bacteria.

Meningococcus is classified into subgroups according to the immunoreactivity of the capsular polysaccharide. While there are at least 13 serogroups, most cases of meningococcal disease are caused by subgroups A and C for which a polysaccharide vaccine is effective. A vaccine has not been produced for subgroup B because the capsule polysaccharide is only poorly immunogenic in humans. In more recent years there have been increasing outbreaks of serogroup Y. Risk factors for meningococcal infection include close contact with carriers or infected individuals, low socio-economic status, poor housing and impairments of both humoral and cell-mediated immunity.

Clinical manifestations of meningococcal infection may develop within minutes or hours. In approximately 40% of patients there is isolated meningitis; 10% have septicaemia alone and the remainder a mixed pattern. Isolated meningococcal meningitis carries a better prognosis than meningococcal septicaemia or mixed picture. Clinically, fulminant meningitis is characterized by pyrexia, headache and meningism associated with nausea and vomiting, photophobia and progressive lethargy. In early meningococcal meningitis there is a diffuse erythematous macular papular rash which eventually develops into the characteristic petechiae found across the trunk and lower extremities in the mucous membranes, conjunctiva and occasionally on the palms and soles. These lesions should be distinguished from other infective disorders that cause a purpuric rash, including enterovirus meningitis and bacterial endocarditis. The development of meningococcal septicaemia is associated with progressive vasomotor disturbance culminating in profound hypotension, tachycardia and a rising respiratory rate indicating pulmonary oedema or raised intracranial pressure resulting from cerebral oedema.

Waterhouse–Friderichsen syndrome is a form of fulminant meningococcal disease, in which severe septicaemia is complicated by the development of bilateral haemorrhage into the adrenal glands and disseminated intravascular coagulation leading to the development of severe sudden febrile illness associated with septic shock, petechiae, purpura and coma.

Management (Table 8.4)

Patients with probable fulminant meningococcal meningitis should be treated immediately with parenteral benzylpenicillin (2.4 g) given intramuscularly or preferably intravenously because of uncertain absorption in patients with shock. If patients are allergic to penicillin they should be given ceftriaxone, cefotaxime or chloramphenicol and transferred immediately to the accident and emergency department. Antibiotics should be given prior to any diagnostic procedure if there is a petechial or purpuric rash or shock. If there is meningitis of uncertain aetiology or if the patient is allergic to penicillin it is preferable to give ceftriaxone 2 g i.v. stat, alternatively cefotaxime or vancomycin can be used.

Septicaemic shock should be treated with appropriate volume replacement, elective intubation and ventilation. Patients may require inotropic support and metabolic abnormalities, coagulopathy and anaemia should also be appropriately treated. In the presence of raised intracranial pressure it may be necessary to administer mannitol, muscle relaxation and appropriate intensive care nursing.

Contacts

Meningococcal meningitis is a notifiable disease in the UK and there is a high risk of family members developing the disease. All household close contacts should therefore be treated to eradicate nasopharyngeal carriage. It is recommended that rifampicin 600 mg 12 hourly should be given as prophylaxis for 2 days, ciprofloxacin 750 mg as a single dose is also effective.

Immunization

Meningococcal vaccination is currently available and contains polysaccharides to serogroups A, C, Y and W135. The beta serotype is antigenically identical to human brain and is therefore poorly immunogenic. The vaccine induces protection for 3–5 years and may be of value in controlling outbreaks.

Outcome

The mortality is approximately 10% although this rises to 40% in those with meningococcal septicaemia coexisting with meningitis. Up to 20% may have neurological sequelae including hearing loss, loss of the limbs secondary to large vessel vasculitis and neurological disability resulting from cerebral ischaemia.

Streptococcus pneumoniae (pneumococcal meningitis)

This the most common cause of meningitis in adults over the age of 18 years with a case fatality rate of approximately 20%. The organism is a Gram-positive coccus; spread occurs by respiratory droplet infection. The primary site of colonization is the nasopharynx and the carrier state is common. *S. pneumoniae* meningitis is commonly caused by local extension from otitis media, or a paranasal source of infection, following a skull base fracture or sinus injury with dural tear. Other predisposing features include pneumonia, alcoholism, diabetes, immunodeficiency states (e.g. splenectomy, hypogammaglobulinaemia, HIV). Clinical presentation is similar to other forms of pyogenic meningitis but a coexisting pneumococcal pneumonia may be present. The course may be aggressive with rapid progression to coma and respiratory arrest. Residual neurological sequelae are common and occur in more than 35% including cerebral oedema, hydrocephalus, vasculitis, venous thrombosis, ventriculitis, labyrinthitis and spinal cord involvement.

Management

The treatment of pneumococcal meningitis has been complicated by the development of penicillin and cephalosporin resistant strains. Conventional treatment is with penicillin, ampicillin and ceftriaxone or cefotaxime but if penicillin-resistant pneumococcal infection is suspected then vancomycin should be added. However, vancomycin itself only crosses the blood–brain barrier poorly and therefore should not be used in isolation. At present, vaccination is inconsistent in inducing adequate immunity and does not include coverage for penicillin-resistant strains of *Pneumococcus*. Failure to improve despite antibiotic treatment implies either the development of cerebral complications, a persistent primary focus or an inadequate or inappropriate dosage of antibiotics. Adjuvant dexamethasone (10 mg 6-hourly i.v. for 4 days) improves the outcome and should be commenced before or with the first dose of antibiotics.

Haemophilus influenzae

This is a small Gram-negative coccobacillus. Prior to the introduction of *Haemophilus influenzae* type B (HiB) vaccination this was the most common cause of meningitis in children with a fatality rate of approximately 5% and permanent neurological damage in some 30% of cases. Meningitis occurs as a consequence of respiratory droplet spread and adults remain vulnerable to the non-encapsulated strains. Risk factors include otitis media, head trauma, previous neurosurgery or a CSF leak. Presentation may be with acute meningitis but an associated vasculitis may occur, leading to focal signs.

Management

The primary treatment of *Haemophilus influenzae* is ceftriaxone or cefotaxime because of the significant incidence of penicillin resistant strains in up to 40%. Chemo-prophylaxis is recommended as single doses for 4 days. Vaccination is recommended for all children with the first dose being given at 2 months.

Listeria monocytogenes

This is a beta haemolytic Gram-positive rod with 12 subtypes based on antigenic properties. It is an intracellular pathogen that lyses phagocytic cells before entering the bloodstream. The overall case fatality rate may reach 15%. Outbreaks are associated with contaminated food including soft cheese, unpasteurized milk and occasionally raw meat. Predisposing factors include pregnancy, advanced age or immunosuppression, and *Listeria* is particularly common in patients with malignancy, renal failure or following organ transplantation or steroid treatment. *Listeria* may cause a meningitis or meningo-encephalitis but seizures, disturbances of consciousness and movement disorders may also occur. A brainstem encephalitis develops in >10%, this presents with a prodromal phase followed by progressive ponto-medullary involvement with cranial neuropathy, pyramidal and sensory signs. The differential diagnosis of brainstem meningitis is listed in Table 8.5.

Management

Treatment is with ampicillin or penicillin for 3–4 weeks although gentamicin is often added to enhance bacteriocidal activity. If there is a penicillin allergy then co-trimoxazole (Septrin) is recommended but chloramphenicol and gentamicin should be avoided.

Group B streptococcus

Group B streptococcus is an important cause of neonatal sepsis and meningitis, it also causes purulent meningitis in adults with

Table 8.5 Differential diagnosis of brainstem encephalitis.

Virus	Enterovirus, EBV, CMV Tick-borne encephalitis
Bacterial	*Listeria, Mycoplasma* *Coxiella, Legionella, Brucella* *Borrelia*
Non-Infectious	Multiple sclerosis Sarcoidosis Acute disseminated encephalomyelitis Vasculitis Carcinomatous meningitis Fisher syndrome

CMV, cytomegalovirus; EBV, Epstein–Barr virus.

a case fatality rate of approximately 5%. Risk factors in neonates include premature birth or low birth weight, prolonged rupture of membranes, intrapartum fever or maternal group B streptococcus infection during pregnancy. In non-pregnant adults, group B streptococcal meningitis is associated with advanced stage diabetes, cirrhosis and systemic malignancy; it is usually acquired nosocomially. The treatment is with penicillin or ampicillin.

Gram-negative meningitis

Gram-negative meningitis (excluding *N. meningitidis*) may arise spontaneously, when the onset is often acute, and the condition follows an aggressive course. More commonly, Gram-negative meningitis may follow neurosurgical intervention when the development and progression is insidious and gradual. Nosocomial infection is usually caused by *Klebsiella* (approximately 40%), *Escherichia coli* (<30%) or *Pseudomonas aeruginosa* (<20%) with *Serratia*, *Enterococcus*, *Proteus* and *Salmonella* meningitis occurring less commonly. Meningitis may be associated with seizures, confusion and focal signs including cranial nerve palsies. The diagnosis is made on CSF culture but this is only helpful in <50% of untreated patients. The limulus lysate assay can detect endotoxin but is limited in sensitivity and has little clinical role. Treatment is with third generation cephalosporin (Table 8.4).

Gram-positive meningitis

Gram-positive meningitis excludes *S. pneumoniae*, but includes neonatal meningitis caused by streptococcus group B. Gram-positive meningitis usually results from a CNS shunt infection but may occur spontaneously in approximately 13% of community-acquired meningitis caused by *Staph. aureus* or streptococcus groups A, B and D. Gram-positive organisms are a common cause of nosocomial shunt infection, usually resulting from *Staph. aureus*, *Staph. epidermidis* or, less commonly, coagulase-negative staphylococci. Spontaneously occurring *Staph. aureus* meningitis may be predisposed by coexisting disease including diabetes mellitus, carcinomatosis, alcohol and intravenous drug abuse. It is usually associated with a focus of infection outside the CNS, e.g. endocarditis or osteomyelitis. The diagnosis is made on the basis of CSF staining and culture. Treatment depends on drug resistance. For fully sensitive staphylococcus, treatment with flucloxacillin is appropriate with vancomycin being used for methicillin resistant *Staph. aureus* (MRSA). There is a high mortality rate of <50% with >10% experiencing neurological sequelae.

Meningitis of unknown aetiology

The initial choice of antibiotic treatment depends on the age of the patient and any underlying risk factors. In the neonate in whom there is a possibility of group B streptococcal infection or *Listeria*, then ampicillin and ceftriaxone should be administered. For anyone over the age of 3 months, ceftriaxone is the preferred treatment; cefotaxime is an alternative. Vancomycin should be given if there is a significant risk of *Strep. pneumoniae* penicillin resistance. In those over 50 years, because of the incidence of *Listeria*, ampicillin is indicated. In patients who are allergic to penicillin or cephalosporins, chloramphenicol remains the drug of choice.

Focal CNS infection

Cerebral abscess

This is a focal suppurative (pus forming) infection occurring within the cerebral parenchyma. It develops as a result of contiguous spread of infection from paranasal sinuses, mastoiditis, otitis media, osteomyelitis or following postoperative and post-traumatic infections. Less commonly, it may arise as a result of haematogenous spread from distant sites including teeth and lungs. However, no cause is found in up to 20% of patients.

The causative agents depend on the underlying abnormality, and the age and immunological status of the patient. These are summarized in Table 8.6. Cerebral abscesses that arise from dental, frontal or ethmoid sinuses tend to involve the frontal lobe while those arising from the sphenoid sinuses or otitic infection particularly involve the temporal lobes. Cerebral abscesses

Table 8.6 Microbiological pathogens in brain abscesses.

Source	Pathogens
Paranasal sinuses, otitic, mastoiditis or dental infection	*Streptococcus* (esp. *Strep. milleri*) 60–70%
	Enteric bacteria (*E. coli, Proteus, Pseudomonas*) 20–40%
	Bacteroides
	Multiple organisms including *Listeria, Clostridium, Fusobacterium* and *Actinomyces*
Post-neurosurgery and penetrating head injury	*Staphylococcus*
	Streptococcus
	Pseudomonas
	Enterobacter
	Clostridium
Pulmonary	*Streptococcus*
	Fusobacterium
	Actinomycosis
UTI	*Pseudomonas*
	Enterobacter
Endocarditis	*Streptococcus viridans*
	Staphylococcus aureus
Immunocompromised (Immunosuppressant medication, diabetes mellitus, iv drugs)	*Pseudomonas*
	Enterobacteriaceae
	Listeria
	Fungi – *Cryptococcus*
	Candida
	Aspergillus
	Nocardia
HIV	*Toxoplasma gondii*
	Mycobacterium tuberculosis
	Cryptococcus neoformans

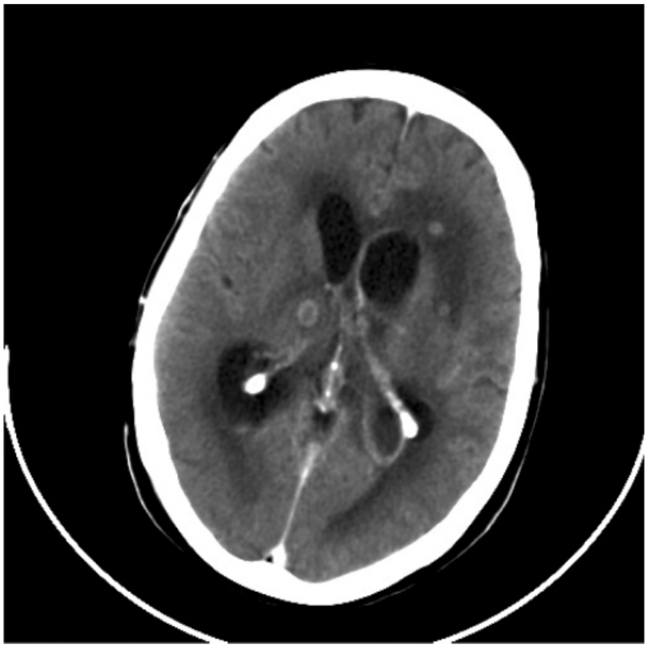


Figure 8.1 Multiple bacterial abscesses and ventriculitis in a 53-year-old woman with Gram-negative septicaemia (enhanced CT).

resulting from haematogenous spread tend to occur as multiple rather than single abscesses (Figure 8.1), often in the region of greatest blood flow, within the basal ganglia.

Clinical features

The peak frequency is 35–45 years but they can occur at any age. Although the characteristic onset is with the subacute or indolent onset of fever, headache, nausea, vomiting, seizures or focal neurological signs, there may be a more rapid onset of neurological symptoms suggesting a space-occupying lesion or cerebral infarction. Fever is variable and may be absent in up to 50% of patients usually those who are older; it tends to resolve rapidly with steroids. Rupture of an abscess into the ventricles may manifest as a severe headache and developing signs of meningism.

Investigation

Routine haematology and biochemistry usually shows an elevation of the erythrocyte sedimentation rate (ESR), white cell count and blood cultures are only positive in about 10%. Computed tomography (CT) scan may show a thin enhancing ring of uniform thickness with smooth margins which tends to be thicker nearer the cortex and thinner near the ventricles. Magnetic resonance imaging (MRI) with enhancement is more sensitive and will document the extent of surrounding oedema more accurately. Lumbar puncture is contraindicated in patients with mass lesions.

Prognosis

The prognosis depends on the clinical state of the patient. Survival is excellent for those fully alert and conscious but declines to 40% if they are unrousable at assessment. Intraventricular rupture carries a mortality of up to 80%.

Table 8.7 Antibiotic treatment of cerebral abscess.

Unknown source	Antistaphylococcal (flucloxacillin or vancomycin) + metronidazole ceftrioxone, ceftaxime (or chloramphenicol)
Streptococci or other Gram-positive (excluding staphylococcus)	Penicillin, ceftrioxone, ceftaxime
Streptococcus (resistant)	Vancomycin
Staph. aureus if MRSA	Vancomycin
Gram-negative organisms (excluding *Pseudomonas aeuruginosa*)	Ceftriaxone, ceftaxime
Pseudomonas aeruginosa	Ceftaxime
Bacteroides	Metronidazole

Treatment

Treatment is urgent, necessitating administration of appropriate antibiotic with surgical drainage or removal and control of cerebral oedema (Table 8.7).

Surgical intervention

Pus evacuation using modern image guidance techniques usually utilizing a mini-craniotomy is the optimum method and carries a low risk, provides a microbiological diagnosis and helps treat the patient. Simple pus aspiration is easier than abscess excision and carries a smaller risk of subsequent seizures but there is an incidence of recurrence even with modern antibiotics. The associated cerebral oedema should be treated appropriately with dexamethasone, hyperventilation and mannitol.

Subdural empyema

Subdural empyema occurs when an intracranial suppurative process develops between the dura and the arachnoid (Figure 8.2). This usually occurs as a consequence of ear or sinus infection, particularly involving the frontal ethmoid sinuses but it is also associated with cranial osteomyelitis, penetrating head trauma, neurosurgery, infection of the subdural effusion in childhood meningitis and, rarely, haematogenous spread.

Pathophysiology

Infection gains entry to the subdural space by direct extension through the bone and dura (e.g. ear and sinus infection, cranial osteomyelitis, penetrating head trauma) or by spread from septic thrombosis of the venous sinus particularly the superior sagittal sinus. Rarely, subdural empyema may result from metastases from infected lungs by haematogenous spread.

Causative agents

Infection is usually secondary to sinus disease from *Streptococci viridans* and aerobic streptococci (*Strep. milleri*) or bacteroides.

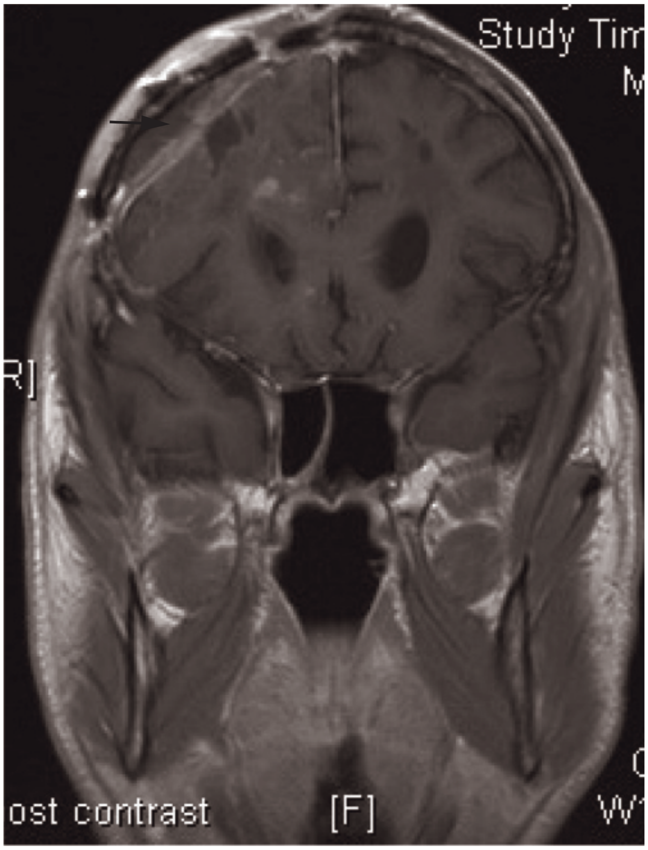


Figure 8.2 Large subdural empyema following previous craniotomy for grade II glioma (MRI T1W).

Less often subdural empyema may be caused by *Staph. aureus* or *Enterobacter* species including *Proteus*, *Klebsiella*, *E. coli* and *Pseudomonas*. However, no organism is found in <50% of patients.

Clinically there is an acute onset with rapid progression to extensive hemispheric involvement or mass effect with tentorial herniation, occasionally a more gradual meningitis may evolve lasting up to 3 weeks. The onset is with pyrexia >80%, localized cranial pain, focal or generalized headache but meningism may develop and focal neurological deficits evolve into hemiparesis. Seizures occur in <50% of patients and there may be progressive obtundation. Venous extension of the infection may lead to the development of meningitis, brain abscess or septic intracranial venous thrombosis. CT scanning may fail to show the collection and the diagnosis is made on the basis of MRI scan with enhancement. The management is immediate surgical decompression with antibiotic cover although there is debate about whether to undertake craniotomy drainage or multiple burr holes. Because many patients with empyema contain a mixed culture of organisms, two or more antibiotic agents are required. For initial therapy where no information exists on the source of infection vancomycin, ceftriaxone and metronidazole are recommended and treatment should be continued for at least 4 weeks. The outcome of surgically treated subdural empyema and intracerebral abscess has been transformed by modern (image-guidance) surgical techniques and antibiotics.

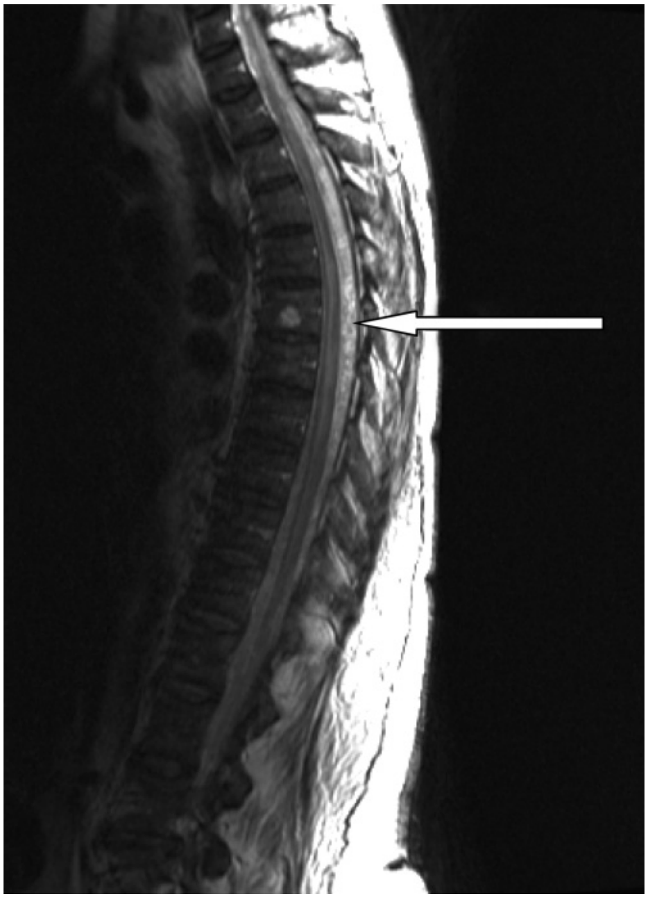


Figure 8.3 Extensive posterior epidural abscess (MRI T2W) (arrow).

Intracranial epidural abscess

Intracranial epidural abscess develops as a result of infection between the outer most layer of the meninges (dura) and the overlying skull. They are associated with cranial osteomyelitis complicating ear, sinus or orbital infection or neurosurgical intervention, infection is rarely metastatic. Epidural abscesses are commonly caused by *Strep. milleri.* The diagnosis and management are similar to subdural empyema. The onset is acute or more insidious after onset with localized cranial pain following generalized headache. The abscess may be accompanied by superficial subcutaneous infection and oedema. Patients develop focal or generalized seizures, focal neurological deficit or alterations in their mental state. Epidural abscess near the petrous bone affecting the V and VI cranial nerve may cause Gradenigo syndrome characterized by unilateral facial pain and lateral rectus weakness. Extension inwards across the dura, along the emissary veins leads to subdural empyema, meningitis, brain abscess or venous sinus thrombosis. Imaging may be normal. Epidural abscesses can be managed by antibiotics alone, following the guidelines indicated above but larger abscesses require surgical drainage.

Spinal epidural abscess

Spinal epidural abscess is an infection of the epidural space of the spinal cord (Figure 8.3). It is usually caused by osteomyelitis or metastatic spread of infection from injuries to the back associated with skin wounds, bacteraemia or septicaemia. It may rarely occur following spinal surgery, lumbar puncture or epidural/spinal anaesthetic. Patients present with fever and back pain which may be severe and localized or radicular. There may be rapid progression with progressive spinal cord compression leading to paraparesis, sensory loss and sphincter involvement with localized spinal tenderness. Rarely, there may be a more chronic and indolent onset with a history suggesting a spinal cord neoplasm.

Staph. aureus is the most common cause of spinal epidural abscess in 50–90% of patients, although a few may be caused by aerobic streptococcus, Gram-negative bacilli and anaerobic organisms. CSF shows a clear pleocytosis but this is usually modest with <100 white cells/mm^3 and these may be both polymorphonuclear and lymphocytes. The protein is usually relatively high. Surgical treatment with laminectomy and drainage is indicated. There is a danger of vascular compromise to the cord causing infarction and permanent cord injury. Recovery may be slow with residual incomplete cord compression caused by formation of the fibrous and granulomatous reaction at the operative site.

Subdural spinal abscess

Subdural spinal abscess may be acute or chronic and caused by osteomyelitis or metastatic spread of infection and may be impossible to distinguish from the more common epidural infection. Presentation is similarly with fever, back and neck pain and rapidly developing signs of spinal cord compression. The onset is variable and may be over days or weeks. The causative agent is *Staph. aureus* in >50% of patients. A clue to the presence of subdural empyema comes from imaging, which tends to show that these lesions have a less sharp margin and a greater vertical extent than epidural abscess.

Spinal cord intramedullary abscess

Spinal cord intramedullary abscess is rare. It may present with a syringomyelia-like picture. The spinal cord is usually involved by direct spread from a contiguous abscess in the skin or if there is spinal dysraphism leading to an open track. Surgical drainage may be necessary.

CNS tuberculosis

Tuberculous meningitis

Mycobacterium tuberculosis is an aerobic non-spore forming bacillus which may be cultured and stained by Ziehl–Neelsen stain. Infection occurs by person-to-person droplet spread. The organism is inhaled into the lower portion of the lungs and there multiplies locally before disseminating through lymphatic and haematological spread into other organs. The decline in incidence of tuberculosis in Europe has led to a marked reduction in the incidence of tuberculous meningitis but unfortunately the condition is still frequent in developing countries and in patients who are immunosuppressed, particularly because of HIV. Tuberculous meningitis develops secondary to a caseating tuberculous focus adjacent to the CSF (Rich Focus). These usually develop following prior haematogenous dissemination of mycobacteria and in the absence of pulmonary tuberculosis. Parenchymal tuberculosis occurs as a result of haematogenous spread and may develop in the absence of pulmonary tuberculosis. Tuberculous meningitis is characterized by inflammatory meningeal adhesive exudates leading to a florid small and medium vessel vasculitis which culminates in occlusion of cerebral arteries and infarction (Figure 8.4a). There is also a disturbance of CSF flow because of impairment of absorption at the arachnoid villi and blockage at the aqueduct and fourth ventricular outlet. In tuberculous meningitis, vasculitis particularly affects the vessels at the base of the brain including the internal carotid, proximal middle cerebral and perforating vessels to the basal ganglia and internal capsule. Tuberculous meningitis was almost invariably fatal before the development of antituberculous chemotherapy. Table 8.8 summarizes factors of prognostic significance in the outcome of CNS tuberculosis.

Clinical manifestations

Tuberculous meningitis is often preceded by a prolonged prodrome of non-specific malaise, anorexia, low-grade fever, myalgia, photophobia and headache. The development of meningitis may be insidious, associated with worsening headache, nausea, vomiting, focal or generalized seizures and progressive impairment of consciousness. Cranial nerve palsies are common and often initially involve eye movements resulting from III, IV or VI nerve palsy. There may be facial weakness (VII), optic neuropathy (II), progressive hearing loss (VIII) and eventual bulbar involvement (X–XII). Fundal examination may show papilloedema,

Table 8.8 Poor prognostic factors in tuberculous meningitis.

Disease severity
Impairment of consciousness
Presence of neurological deficits, seizures or abnormal movements
Extremes of age
Coexisting miliary disease
CSF protein with spinal block
Very low CSF glucose
CT scan showing abnormalities
HIV positive, low CD4 count (below 22/mm^3)
Illness longer than 14 days

CSF, cerebrospinal fluid; CT, computed tomography.

optic atrophy or the presence of choroidal tubercles. Visual impairment may also develop because of involvement of the optic chiasm, tuberculomas compressing the optic pathways or optic nerve toxicity resulting from ethambutol. Other neurological signs include hemiparesis and hemiplegia as a consequence of vasculitic infarction or space-occupying tuberculomas. Movement disorders may be manifest as tremor, myoclonus, chorea, hemibellismus or dystonia and cerebellar ataxia may occur from direct involvement or vasculitic infarction. Cerebrovascular disease usually occurs in the distribution of the anterior circulation but may be posterior in distribution.

Diagnosis

The diagnosis of tuberculous meningitis or focal parenchymatous involvement may be clinically difficult. Tuberculin skin test is variable in its response and unreliable as there may be an anergy even in the presence of miliary tuberculosis. CSF examination is characterized by the presence of lymphocytic pleocytosis with a high protein and low glucose. The white cell count is usually 60–300/mm^3 and should not generally exceed 1000 but there may be a significant proportion of polymorphonuclear cells in the initial stages. The protein is generally elevated up to 1 g/L but may be greater than this particularly if there is a spinal block. There is also a low glucose concentration below 2.2 mmol/L and this is usually at least below 50% of the serum glucose.

CSF bacteriology

Direct examination of the CSF for acid–alcohol fast bacilli (AFB) requires the provision of large volumes of CSF and is experience dependent. AFB are only seen in up to 25% of cases with appropriate staining. CSF culture is the diagnostic investigation but requires up to 6 weeks and is therefore of only limited value in clinical practice. Culture is positive in up to 70% of cases and has the advantage of indicating drug sensitivities if the samples are taken before treatment has commenced. CSF PCR for tuberculosis is a sensitive technique but is limited in its specificity and is difficult to undertake. It is likely to play an increasingly important part in the diagnosis of tuberculous meningitis.

Radiology

Approximately 50% of patients with tuberculous meningitis may show evidence of previous tuberculosis on chest X-ray with up to 10% having miliary tuberculosis. CT brain scanning is commonly abnormal with marked enhancing exudate in the basal cisterns. There may also be hydrocephalus, parenchymal enhancement, evidence of cerebral infarction or cerebral oedema or focal tuberculoma. MRI is sensitive in showing meningeal enhancement, focal parenchymal abnormalities or the development of communicating or obstructive hydrocephalus.

Management of tuberculous meningitis

This is aimed at eradicating the causative organisms and management of the complications caused by the inflammatory response including hydrocephalus, vasculitis and raised intracranial pressure. The standard treatment of tuberculous meningitis is with an intensive primary phase of treatment followed by a continuation phase as summarized in Tables 8.9 and 8.10. Treatment should commence with isoniazid, rifampicin, pyrazinamide and ethambutol for 3 months and this should be followed by a 6-month continuation phase of treatment with isoniazid and rifampicin or pyrazinamide. There remains some debate about the duration of treatment.

Isoniazid and pyrazinamide are bacteriocidal and show good penetration through inflamed meninges, easily achieving therapeutic concentrations. Rifampicin, ethambutol and streptomycin have poorer penetration and achieve lower CSF concentrations.

Table 8.9 Treatment of tuberculosis. Initial phase using four drugs for 3 months.

Drug	Adult dose	Comment	Side effects
Isoniazid	<300 mg	Penetrates CSF freely and has potent early bacteriocidal activity Add pyridoxine to avoid peripheral neuropathy	Hepatitis, haemolytic anaemia, aplasticanaemia, peripheral neuropathy, optic neuritis, mania, fits
Rifampicin	450 mg (wt < 50 kg) 600 mg (wt > 50 kg)	Bacteriocidal but poor CSF penetration (10%)	Hepatitis, thrombocytopenia, headache, confusion drowsiness
Pyrazinamide	1.5 g (wt < 50 kg) 2.0 g (wt > 50 kg)	Bacteriocidal with good penetration	Hepatitis, anorexia, flushing
Fourth drug use one of:			
Streptomycin	<1 g/day	Neither penetrates CSF well in absence of inflammation (10–50%)	Avoid in pregnancy and renal impairment NM blockade
Ethambutol	15 mg/kg/day		Retrobulbar neuritis, peripheral neuropathy, confusion
Ethionamide	500–750 mg/day	Penetrates healthy and inflamed meninges but no evidence of advantage over other drugs	

CSF, cerebrospinal fluid; NM, neuromuscular.

All antituberculous treatment carries significant toxicity. Treatment with a fourth drug during the initial phase remains indicated given the poor ability of streptomycin and ethambutol to cross the blood–brain barrier.

There is an increasing incidence of tuberculosis caused by organisms resistant to conventional treatment. If this is suspected the initial treatment should include at least four drugs followed by a maintenance course of 9–18 months. An alternative aminoglycoside may be used during the initial phase (kanamycin, amikacin or capreomycin), ethionamide or moxifloxacin.

Corticosteroids

Steroids are indicated in the acute phase particularly if there is cerebral oedema, spinal block, severe tuberculous meningitis, spinal arachnoiditis or cerebral vasculitis.

Surgical intervention

Surgical intervention may be required in the presence of obstructive hydrocephalus that has not responded to medical treatment.

Table 8.10 Treatment of tuberculosis. Continuation phase using two drugs for 6 months.

Isoniazid	
Rifampicin	
Pyrazinamide	Achieve high CSF concentrations
Suspected or proven multidrug resistance:	
Aminoglycoside	Kanamycin, amikacin, capreomycin
Ethionamide	
Pyrazinamide	
Ofloxacin, moxifloxacin	

CSF, cerebrospinal fluid.

This usually consists of an an external ventricular drain initially but may eventually necessitate a ventriculo-peritoneal shunt.

Outcome

The outcome of tuberculous meningitis has remained poor and the mortality is still >20%, with severe neurological sequelae occurring in up to 30% of survivors. Early drug treatment is essential particularly before the development of impaired consciousness and coma. Late neurological disability is predicted by the presence of extrameningeal tuberculosis, cranial nerve palsies, limb weakness and multiple neurological abnormalities.

Parenchymal CNS tuberculosis

Tuberculous granuloma (tuberculoma)

Tuberculous granulomas can be found in the cerebrum, brainstem, cerebellum, spinal cord, subarachnoid or epidural space but are generally supratentorial; they may be multiple in up to two-thirds of patients and may coexist with tuberculous meningitis in up to 10% of patients. They present as space-occupying lesions with headache, intracranial hypertension, seizures and papilloedema. Imaging confirms the presence of an enhancing space-occupying lesion, occasionally with central calcification (Figure 8.4b and c). They usually resolve with conventional antituberculous treatment but occasionally surgical intervention is indicated.

Tuberculous abscess

Tuberculous abscess results from liquifaction of the central core of the tuberculoma. The lesions often enlarge and become multilocular and have mass effect associated with oedema. They tend to resemble pyogenic abscesses rather than tuberculomas and may be difficult to distinguish clinically. They do not always respond well to antituberculous chemotherapy and surgical excision may be necessary.

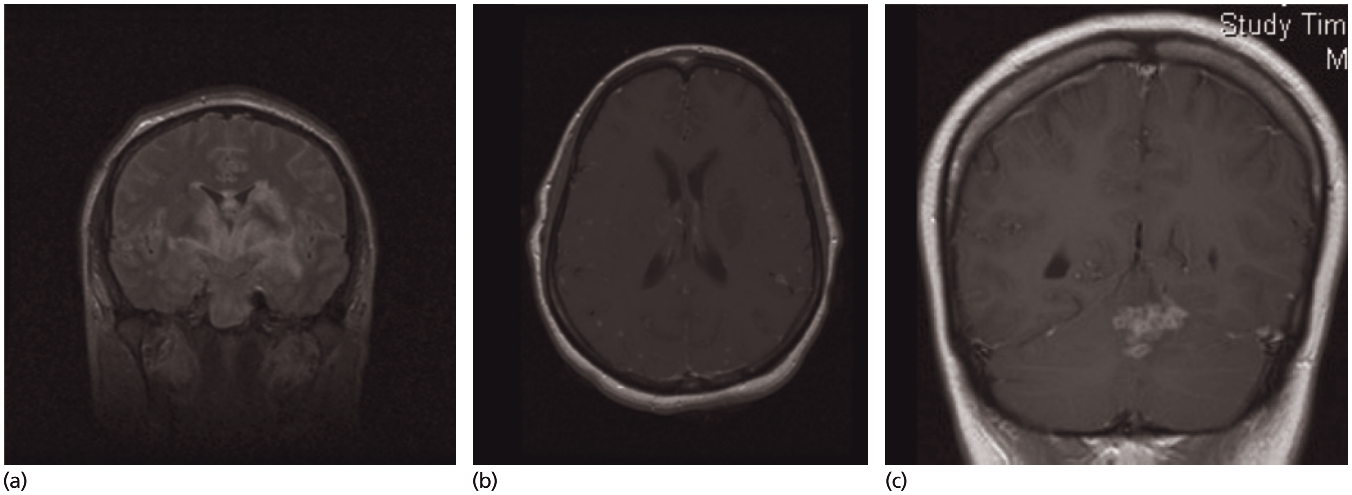


Figure 8.4 (a) Extensive vasculitis associated with tuberculous meningitis (MRI T1W). (b) Multiple tuberculomas (MRI T1W). (c) Multiple tuberculomas (MRI T1W).

Spinal tuberculosis (tuberculous spondylitis)

Tuberculosis may involve the spinal vertebral bodies, with a predilection for the anterior elements (Figure 8.5). In adults at least two contiguous levels and their intervening disc space are involved, particularly in thoracic and lumbar regions. Paraspinal soft tissue involvement is common and a paravertebral tuberculous abscess (Pott's abscess) may occur in up to 30% of patients with tuberculous spondylitis. Spinal collapse is also frequent and leads to cord compression and paraparesis.

Tuberculous spinal meningitis may be localized to the spinal cord. In this condition there is a gross granulomatous exudate in the subarachnoid space, which causes a vasculitic response in the spinal vessels, particularly the anterior spinal artery, culminating in ischaemia or infarction of the spinal cord. There may also be a progressive radiculopathy, myelopathy or transverse myelitis. Intramedullary spinal cord tuberculous abscess or, rarely, tuberculoma may occur within the substance of the spinal cord mimicking a tumour. Tuberculous radiculomyelopathy or transverse myelitis often present acutely but may be slower in onset. They may be characterized by radicular pain, bladder disturbance or progressive paraparesis. CSF shows a high protein content with lymphocytic pleocytosis and a low glucose. MRI scan shows contrast enhancements surrounding the spinal cord and roots and often a diffusely increased intramedullary signal. Spinal cord disease is treated with prolonged standard antituberculous treatment and systemic steroids. If there is significant bone destruction, bracing and/or surgical decompression and stabilization may be necessary.

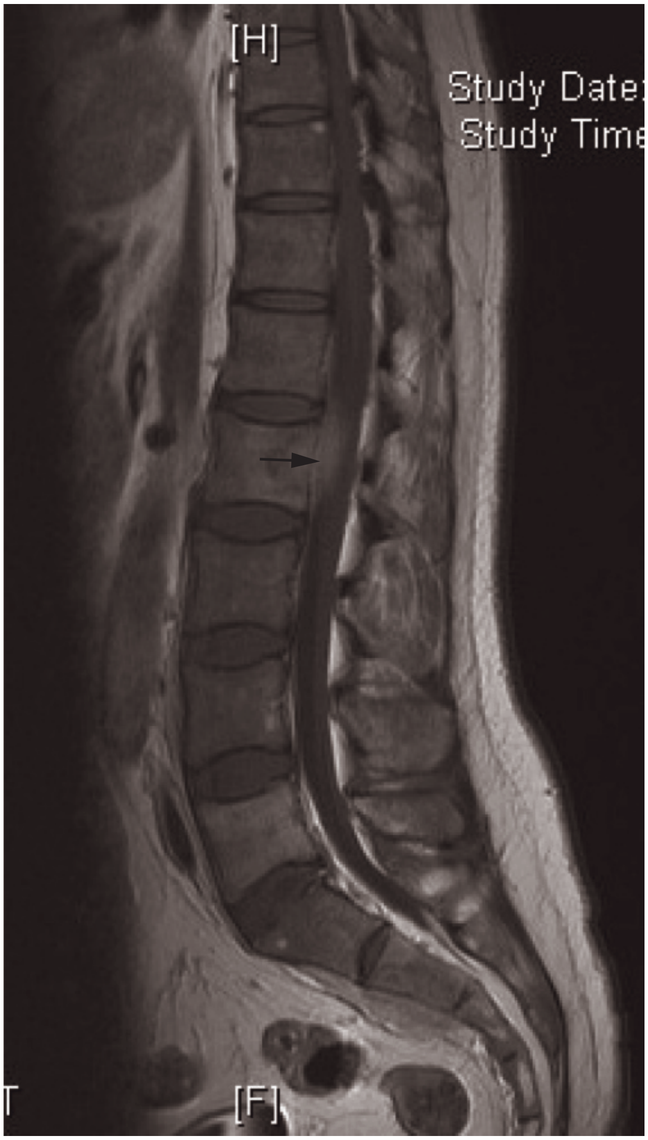


Figure 8.5 Anteriorly placed tuberculous abscess (MRI T1W) (arrow).

Syphilis

Syphilis is a chronic systemic infection caused by *Treponema pallidum*. The organism is a long slender coiled spirochete that is actively motile and sexually transmitted. It readily penetrates intact mucus membranes and abraded skin, rapidly reaching the bloodstream and lymphatics.

Syphilis is characterized by three stages:

1 Local primary chancre;

2 Secondary bacteraemic state with generalized mucocutaneous lesions; and

3 Tertiary stage characterized by involvement of the heart, bone, skin and CNS.

Primary syphilis usually develops within a few days of exposure but may be delayed up to 90 days. It is characterized by an ulcerated painless chancre at the site of inoculation with local lymphadenopathy. Manifestations of secondary syphilis usually develop 6–12 weeks after the chancre heals and consist of a characteristic generalized maculopapular rash involving the palms and soles which is associated with a diffuse generalized lymphadenopathy and constitutional symptoms including fever, weight loss and malaise. There may also be an associated proctitis, hepatitis, gastritis, nephrotic syndrome and iridocyclitis. Secondary syphilis is associated with neurological involvement characterized by meningitis and focal signs including multiple cranial nerve palsies, acute optic neuritis, sensori-neural hearing loss, aphasia, hemiplegia and focal epilepsy. The infection then becomes latent with a prolonged quiescent phase. Approximately one-third of untreated patients with latent syphilis develop tertiary disease and <10% develop symptomatic neurosyphilis.

Meningo-vascular syphilis

Meningo-vascular syphilis develops within 10 years of infection and is caused by an obliterative endarteritis and periarteritis associated with meningitis which may affect the brain or spinal cord. Progressive impairment of CSF absorption may lead to hydrocephalus, manifest as headache or confusion, there may be signs of focal cortical involvement including aphasia, hemiplegia, hemisensory disturbance or multiple cranial nerve palsies leading to diplopia, vertigo and dysarthria. Spinal cord involvement in the form of a meningo-myelitis is characterized by the slow evolution of a spastic paraparesis with sensory disturbance in the lower limbs and bowel and bladder involvement. There may also be a more acute transverse myelitis with patchy cord involvement and anterior spinal cord artery occlusion may occur.

Tabes dorsalis

Tabes dorsalis occurs in 35% of those with neurosyphilis <10 years after primary infections. There is involvement of the posterior columns with diffuse infiltration and atrophic change. Symptoms include characteristic lightning pains in the legs which consist of sharp shooting paraesthesiae and pain and tabetic crises of episodic acute abdominal pain. The proprioceptive impairment leads to severely ataxic gait with a characteristic stamping of the foot. There is also impaired deep pain sensation with bladder, bowel and sexual dysfunction. Progressive posterior column impairment leads to the development of Charcot joints, a severe destructive arthropathy caused by repeated trauma, ulcers may develop around these joints. Cranial nerve abnormalities are associated with tabes including optic atrophy and pupillary abnormalities.

General paralysis

General paralysis is caused by direct invasion of the brain by spirochetes leading to frontal and temporal atrophy; it develops >15 years after the initial infection. There is a progressive cognitive impairment with memory loss and disintegration of personality and behaviour leading to severe dementia. This is associated with psychiatric disturbances including emotional lability, paranoia, delusions of grandeur and hallucinations. There may be a characteristic coarse tremor of the tongue and similar tremor of the extremities with pyramidal signs including hyper-reflexia. Pupillary abnormalities are characterized by the Argyll Robertson pupil in which the accommodation reflex is preserved but absent response to direct light.

Syphilis may be associated with HIV and progression to neurosyphilis may occur earlier.

Diagnosis

In primary and secondary syphilis, diagnosis is usually undertaken with dark field microscopy from skin and mucous membranes allowing direct visualization of the spirochete. The diagnosis of neurosyphilis depends on serological tests which may be either non-specific antigen tests (Venereal Disease Research Laboratory [VDRL] and rapid plasma reagin [RPR]) or specific treponemal tests (fluorescent treponemal antibody absorption, microhaemagglutination assay and the treponemal immobilization test). Specific treponemal tests are very reactive in secondary, latent and tertiary syphilis. They remain positive regardless of the disease stage and treatment. The presence of a positive VDRL on CSF examination may indicate neurosyphilis but there is a high incidence of false negative findings (particularly because of previous infection with yaws) and therefore the definite diagnosis depends on the presence of a positive serum treponemal test and a reactive CSF with pleocytosis, increased protein and IgG and possibly also oligoclonal bands. Co-infection with HIV also complicates the diagnosis as the CSF abnormalities may be unrelated to the neurosyphilis.

Treatment

Treatment of neurosyphilis is with benzylpenicillin 2.4 g given i.m. at weekly intervals for 3 weeks but the CSF penetration is variable and it may be necessary to continue for a longer period if the infection is incompletely cleared. As an alternative to parenteral treatment, amoxicillin 3 g 12 hourly can be given orally together with probenecid. If patients are allergic to penicillin, erythromycin 500 mg 6 hourly is recommended but tetracycline and ceftriaxone 2 g for 10 days are alternatives. Early treatment of syphilis may be associated with a Jarisch–Herxheimer systemic reaction which occurs because of the rapid destruction of treponemes and is characterized by sudden onset of severe systemic features including fever, chills, headache and tachycardia. All patients being treated for syphilis should be pretreated with prednisolone 60 mg for 24 hours. The CSF should be re-examined after treatment has been completed to show a fall in the pleocytosis and then at 6-monthly to 1-year intervals until the cell count and protein levels have returned to normal.

Lyme disease (neuroborreliosis)

Borrelia burgdorferi is a helical motile Gram-negative spirochaete. The substantial clinical differences between infections in the USA and Europe arise as a result of the differing strains – *B. burgdorferi sensu stricto* in North America and *B. garnii* and *B. afzelli* in Europe and Asia. The infection is a zoonosis in which the spirochaete is maintained in populations of large and small mammals, such as deer, field mice, as well as birds and spread by the ixodid tick. In Europe, Lyme disease is a significant problem in Germany, Austria, France, Switzerland and Sweden where the annual incidence maybe as high as 69/100,000. In the UK, the south-west regions are endemic areas. In North America most cases occur in the north-east and mid-Atlantic regions, with 15,000 cases reported each year. Lyme also occurs in Asia. Russian cases are well documented. Lyme disease affects all ages with time outdoors being the most significant risk factor, e.g. forest workers. A travel, occupational and social history with regard to hobbies such as shooting and rambling is therefore crucial. The infection occurs between May and September when the tick feeds, as they become inactive in cold weather.

Early neuroborreliosis – clinical features

Local infection

After a tick bite, 50–90% of patients develop the pathognomic skin lesion erythema migrans (EM), 7–10 days later. Typically, the lesion is not painful or pruritic and enlarges centrifugally over the ensuing days. The rash may be accompanied by systemic

Table 8.11 Clinical spectrum of Lyme disease.

Infection stage	Incubation period	Clinical features
Early local infection	<1 month	Erythema migrans, lymphocytoma cutis, flu-like illness, headache
Early disseminated infection	<3 months	Multifocal EM, arthritis, myalgias, myositis, cardiac (conduction block, pericarditis, myocarditis) conjunctivitis Meningitis, meningoencephalitis, cranial neuropathy (VII) acute painful radiculoneuropathy
Late stage	>3 months	Acrodermatitis chronica atrophicans Arthritis Keratitis, uveitis Chronic encephalomyelitis Chronic polyneuropathy ? Motor neurone disease like syndrome

EM, erythema migrans.

symptoms of malaise, fever, headache, meningism, arthritis and lymphadenopathy (Table 8.11).

Early disseminated infection

Haematogenous dissemination within a few days or weeks after the initial inoculation results in a number of complications – cardiac involvement occurs in 5–10% with conduction abnormalities such as complete heart block requiring temporary pacing. The neurological complications described at this stage are an aseptic meningo-encephalitis, cranial neuropathy and a painful radiculoneuropathy, which may all occur in combination. Although some of these early disseminated syndromes may resolve without therapy, 10% will go on to develop late chronic disease that is less responsive to antibiotic therapy, hence the necessity for early diagnosis and treatment. This pattern is similar to that found in neurosyphilis.

Cranial neuropathy

A facial palsy occurs in 50–75% of patients with early disseminated disease. Clues that may lead to the suspicion of Lyme disease related facial palsy are the occurrence of facial palsy during the summer months in endemic areas and associated systemic symptoms such as headache, meningism and arthritis. In one-third, the facial palsy is bilateral. This narrows the differential diagnosis to a limited number of conditions: Guillain–Barré syndrome (GBS), meningitis caused by e.g. HIV, chronic meningitic disorders such as sarcoidosis, malignant meningeal infiltration and amyloidosis. Involvement of the IIIrd, Vth, VIth and VIIIth cranial nerves has also been described.

Acute radiculoneuropathy

This complication is much higher in European Lyme disease compared to that found in North America. Patients present with severe radicular pain, which may affect the limbs or trunk resembling mechanical root pain. Weakness, sensory loss and areflexia develop over the next few days. When acute and severe, the clinical picture may resemble GBS although demyelination on neurophysiological studies is unusual in neuroborreliosis and CSF pleocytosis should raise doubts about the diagnosis of GBS. The differential diagnosis of such a painful radiculoneuropathy with a pleocytic CSF includes herpes zoster with or without a rash (zoster sine herpete), cytomegalovirus infection in the context of immunosuppression, malignant infiltration and sarcoidosis. Peripheral nerve vasculitis should also be considered. In patients with diabetes or those in whom this neurological syndrome may be the first manifestation, proximal diabetic radiculoplexoneuropathy (Bruns–Garland syndrome) and diabetic truncal radiculopathy have similar features.

Other syndromes

Anecdotal reports have described brachial and lumbosacral plexopathies similar to neuralgic amyotrophy (Parsonage–Turner syndrome). A number of patients with the clinical motor neurone disease (MND) phenotype and serological evidence of Lyme disease that have responded to antibiotics suggests that, at least in endemic areas, the diagnosis is worth considering.

Late neuroborreliosis – clinical features

A few untreated patients with early untreated Lyme disease may go on to develop a chronic disorder and, occasionally, this maybe the first presentation of neuroborreliosis. These include:

1 Acrodermatitis chronica atrophicans.
2 Chronic axonal neuropathy. Patients present with distal sensory, radicular involvement or restless legs. Neurological examination is unremarkable with only minor sensory abnormalities on examination. Neurophysiological abnormalities are consistent with a patchy sensory more than motor axonal neuropathy. The CSF is normal. Nerve biopsies are unhelpful but can reveal minimal changes of an axonal neuropathy.
3 Chronic meningitis, progressive myeloradiculopathy or encephalomyelitis.
4 Subacute encephalopathy.

Post Lyme syndrome

Despite effective antibiotic treatment, some patients complain of persistent symptoms of fatigue, myalgia, paraesthesias, memory difficulties and depression. The diagnosis of this post Lyme syndrome remains contentious because of the persistence of positive serological tests after approppriate antibiotic treatment. Management of such patients is therefore focused on symptom control.

Diagnosis

The diagnosis of neuroborreliosis can be difficult for several reasons. The diagnosis remains clinical with laboratory support provided by serological tests and CSF examination. Features worth noting in the history are exposure in an endemic area, albeit brief, and the neurological syndromes are commonly associated with systemic symptoms. The American Academy of Neurology has produced practice parameters for the diagnosis of patients with nervous system Lyme disease (Table 8.12).

Culture is the gold standard but is difficult to achieve. Punch biopsy or aspiration of the EM lesion has the highest positive rates of 40–80%. Less than 10% of CSF cultures are positive reflecting the low density of organisms. Serology provides the basis for the laboratory support of the clinical diagnosis with a number of caveats:

1 The demonstration of positive antibody is evidence of exposure rather than active disease. Furthermore, these will remain positive even after adequate treatment regimens and cannot be used to assess treatment response.

2 Serology may be negative, especially in early disease because IgM antibodies take 2 weeks to develop and IgG antibodies 4–6 weeks after inoculation. Patients prescribed inadequate doses of antibiotics early in the course of the illness may remain antibody negative despite persistence of viable organisms.

3 False positive results may occur because of infections such as syphilis, ricketsial and bacterial infections and autoimmune disorders.

Table 8.12 American Academy of Neurology guidelines for the diagnosis of nervous system Lyme borreliosis.

Diagnosis of definite nervous system Lyme disease requires:

1 Possible exposure (in wooded, brushy or grassy areas) to appropriate ticks in an area where Lyme disease occurs. A history of tick bite is not necessary

2 One or more of the following:
  (i) Erythema migrans, the pathognomonic rash, or histopathologically proven *Borrelia* lymphocytoma or acrodermatitis
  (ii) Immunologic evidence of exposure to *Borrelia burgdorferi* (e.g. positive serology)
  (iii) Culture, histologic or PCR proof of the presence of *B. burgdoferi*

3 Occurrence of one or more of the following neurologic disorders after exclusion of other potential aetiologies. If CNS disease is suspected, CSF should be examined for intrathecal antibody production, culture or PCR

Causally related neurologic disease:
  (i) Lymphocytic meningitis, with or without cranial neuritis or painful radiculneuritis
  (ii) Encephalomyelitis
  (iii) Peripheral neuropathy

CSF, cerebrospinal fluid; PCR, polymerase chain reaction.

The current recommendation is to use a two-tier system for serodiagnosis – screening with an enzyme-linked immunosorbent assay (ELISA) or immunofluorescence assay (IFA) which is rapid and sensitive. Positive tests are followed up by a more specific Western blot analysis. Western blots are considered positive in acute disease if two of three selected bands are positive. In disease of longer duration five out of ten positive bands are required.

CSF examination is abnormal in most cases of neuroborreliosis – the exception being the chronic axonal neuropathy described above. There is usually a lymphocytic pleocytosis of up to a few hundred cells with an elevated protein level. The glucose is usually normal or slightly reduced. Intrathecal antibody production against *B. burgdorferi* is a useful indicator of infection; however, like blood serology, it may be a marker of past infection and remains positive after treatment. It is therefore necessary to assess CSF cytochemical parameters for evidence of active infection or a treatment response. PCR has proved disappointing with less than 50% of patients with meningitis demonstrating a positive response. As with serology, a positive PCR can be a marker of prior infection without viable organisms being present in the CSF.

Treatment

Although early disseminated neurological syndromes may resolve spontaneously, 10% go on to develop the late complications. The current recommendation is that early and late neurological and cardiological borreliosis be treated with intravenous third generation cephalosporins such as ceftriaxone 2 g o.d. for 2–4 weeks. Because it has not yet been determined whether a 2-week course is as effective as a 4-week course it seems reasonable to err on the side of caution. The alternative is another third generation cephalosporin cefotaxime 2 g 8 hourly. which is less convenient. Intravenous penicillin G 3–4 mU six times daily (18–24 mU/day), provided renal function is normal is another alternative. Oral or intravenous doxycycline 100 mg 12 hourly. was found to be effective for neuroborreliosis including meningitis in one European study and is an alternative. It maybe argued that facial palsy is a peripheral disorder and oral antibiotics will suffice. However, many patients have symptoms of meningism and the CSF is abnormal. It is therefore reasonable to consider lumbar puncture in patients presenting with facial palsy in endemic areas before deciding on the most appropriate treatment regimen.

Brucellosis

Brucellosis is a zoonotic infection caused by a Gram-negative non-motile non-encapsulated coccobacilli, *Brucella melitensis* and *B. abortis* (harboured in sheep and cattle, respectively). It is a granulomatous illness which may be acute or indolent. There is a non-specific prodrome with a variable and irregular (undulant) fever and flu-like symptoms of malaise, night sweats, arthralgia and myalgia. The development of lymphadenopathy and hepatosplenomegaly may resolve or be followed by localized single organ infection. The nervous system is affected in up to 5% of patients; meningitis is the most common manifestation with meningism, confusion and impaired level of consciousness. Cranial nerve deficits occur as a consequence of granulomatous involvement at the skull base and facial weakness, sensori-neural hearing loss and visual impairment resulting from retrobulbar neuritis, papilloedema, optic neuropathy or ophthalmoplegia may occur. Brucella meningitis can lead to hydrocephalus and raised intracranial pressure. Brain and spinal cord abscesses can occur. There may be a granulomatous endarteritis or focal vasculitis causing stroke or myelitis, occasionally a radiculopathy and peripheral neuropathy may also occur. Blood cultures are positive in 50% of patients and CSF is positive in 25% on culture or standard agglutination tests. CSF shows an elevated protein with a lymphocytic pleocytosis and a low glucose; occasionally oligoclonal bands are present. MRI may show contrast enhanced inflammatory changes in the spinal cord or brain.

Brucella is treated by a variety of antibiotics including streptomycin, co-trimoxazole, tetracyclines, rifampicin or gentamicin. There is a high relapse rate with single drug treatment leading to drug complications. In particular, brucella meningitis should be treated with three drugs for 2–6 months and surgical drainage of brucella abscesses may be necessary.

Leptospirosis

Leptospirosis is caused by the aerobic spirochete *Leptospira* carried by rats. Although clinical manifestations vary in severity, presentation is gradual and non-specific with a flu-like illness, pyrexia, nausea, vomiting and myalgia. Systemic involvement may rapidly develop with chest and abdominal pain. Aseptic meningitis is characterized by headache, photophobia and meningism progressing to encephalopathy with seizures. Ocular features include conjunctival injection, optic neuritis and uveitis. In the most severe form of the condition (Weil disease) there is hepatic and renal impairment with a bleeding diathesis. Less commonly, leptospirosis may result in acute disseminated encephalomyelitis or cerebrovascular disease manifest as vasulitic ischaemia or haemorrhagic complications. Cranial neuropathy, peripheral nerve involvement including radiculopathy, mononeuritis multiplex and an axonal or demyelinating peripheral neuropathy may occur.

CSF in the meningitic state shows a mononuclear pleocytosis which is usually approximately 100/mm^3 but may rise to >10,000/mm^3. The protein concentration may also be elevated. The diagnosis depends on culture requiring special media and growth is very slow. Diagnosis can also be made by serology, complement fixation and specific agglutination tests.

The meningitic illness is usually self-limiting. *Leptospira* are sensitive to antibiotics during the initial febrile phase and treatment is with intravenous penicillin 6 mU/day or amoxicillin or erythromycin but there is a risk of Jarisch–Herxheimer reaction.

Leprosy

Leprosy is an extremely common condition worldwide, which occurs predominantly in Africa, South America, South-East Asia, Brazil, Mozambique, Nepal, India, China and Madagascar. It is caused by *Mycobacterium leprae* which causes granulomatous involvement of the peripheral nerves and skin. The organism is a Gram-positive rod which is an obligate intracellular acid-fast bacillus. It multiplies at cooler temperature and therefore favours distal parts of the human body. There is a prolonged incubation period ranging 2–5 years but this may be as long as 20 years. The organism has a predilection for Schwann cells associated with thinly myelinated axons. The infective risk of leprosy is relatively low but nasal transmission may occur and is followed by haematogeneous spread to preferential sites including skin, peripheral nerves, upper respiratory tract, anterior chamber of the eye and the testes.

The pattern of illness is determined by the host's immune response to the mycobacterial antigen. When there is an active cell-mediated immune reaction directed against *M. leprae*, tuberculoid leprosy develops that is restricted to a few peripheral nerves. However, a poor immune response leads to an extensive proliferation of bacilli, the so-called lepromatous leprosy. A proportion of patients also have borderline patterns with features of both tuberculoid and lepromatous. The World Health Organization (WHO) uses a simplified classification scheme that relies on clinical examination and skin scrapings, dividing cases into paucibacillary and multibacillary leprosy. Paucibacillary leprosy is defined as five or fewer skin lesions without detectable bacilli on skin smears whilst in multibacillary leprosy there are six or more lesions and skin smear may be positive. The risk of transmission from close contact is much greater in the multibacillary form.

Clinical features

Leprosy is characterized by hypoaesthetic skin lesions, thickened peripheral nerves and positive skin smear showing acid-fast bacilli.

The earliest skin lesions are mildly hypopigmented macules which may heal or evolve into tuberculoid or lepromatous appearances. In tuberculoid leprosy, there are single or few clearly demarcated asymmetrical hypopigmented or erythematous skin lesions which are hypoaesthetic and are scattered across the body with no obvious preferential areas. They have a sharp edge but vary in size. In lepromatous leprosy, there is a more diffuse involvement of the skin with extensive hypopigmented, nodular or maculopapular infiltration affecting the body, the skin of the face and the earlobes, with progressive loss of the eyebrows and eyelashes. There may be coarse thickening of the features, particularly the earlobes, nose and cheeks, giving rise to the characteristic pattern of leonine facies, and the larynx may also be involved. The testes become atrophic and gynaecomastia and sterility may develop. Visual impairment occurs because facial weakness and anaesthesia of the conjunctiva and cornea lead to corneal ulceration and scarring culminating in exposure keratitis. There also may be an iridocyclitis and cataracts secondary to intraocular involvement by the bacilli.

Nerve involvement

In tuberculoid leprosy, there is involvement of the small superficial nerves in the cooler part of the body and at points where they are exposed, leading to pain on temperature, touch and pressure impairment over affected skin areas but thickening is less common. The most frequently affected peripheral nerves are as follows:

- Ulnar nerve;
- Posterior tibial nerve and sural (at the medial malleolous of the tibia);
- Common peroneal nerve – at the knee where it winds around the neck of the fibula;
- Median (at the wrist);
- Facial (crossing zygomatic arch);
- Trigeminal nerve involvement of ophthalmic division of the trigeminal nerve leading to corneal and conjunctival sensory loss, ulceration and blindness;
- Greater auricular (posterior triangle of the neck);
- Supraorbital; and
- Superficial radial (cutaneous at the wrist).

Lepromatous involvement of the peripheral nerves is insidious over many years. Peripheral nerve thickening affects sensory motor and autonomic nerves to a varying extent and may cause either a focal or diffuse mononeuritis multiplex or a progressive symmetrical distal peripheral neuropathy. Sensory impairment is more common than motor but there may be atrophy and weakness leading to claw hands or bilateral foot drop.

Borderline leprosy

There are features or both tuberculoid and lepromatous forms. Hyperanaesthetic skin lesions occur but they differ slightly in appearance from lepromatous leprosy. Borderline patients are particularly vulnerable to nerve damage and may develop severe deformities including trophic ulceration. The affected nerve trunk is often swollen and painful.

Primary neuritic leprosy

This is seen in India and Nepal. This presents as a peripheral neuropathy without the characteristic skin lesions and skin smears are negative for acid-fast bacilli. However, skin lesions develop later in the course of the illness. Neurological manifestations are caused by asymmetrical involvement of one or several peripheral nerve trunks and sensory changes develop before motor features. Isolated nerve thickening may occur.

Diagnosis

This is difficult and primarily clinical although nerve conduction studies show axonal loss and demyelination with focal slowing across thickening nerve segments suggesting segmental demyelination. There is loss of the sensory action potentials. A skin smear is used to assess the density of acid-fast bacilli – they are always found in the multi-bacillary form and occasionally in borderline disease. Skin biopsy is essential for diagnosis, correct classification and diagnosis when skin smears are negative. Nerve biopsy of a thickened sensory nerve (usually sural or radial cutaneous nerve) may also yield a diagnosis. The Lepromin test assesses the patient's cell-mediated immunity against *Mycobacterium leprae* and is strongly positive in tuberculoid leprosy but is negative in lepromatous leprosy; this test is of no value in patients who have received bacille Calmette–Guérin (BCG) vaccination or who have had previous subclinical disease. Serology tests use radioimmune assay (RIA) and ELISA assay based on the detection of antibodies to *M. leprae* antigen. The *M. leprae* genome has now been entirely sequenced and it is possible to detect the organism using PCR amplification in skin and nerve biopsies.

Management

Multi-drug therapy with a combination of rifampicin, dapsone and clofazimine is effective in both multi-bacillary and paucibacillary leprosy and nerve function does appear to improve with early treatment. The skin lesions in paucibacillary leprosy resolve within a year but in patients with multi-bacillary leprosy they persist for much longer but relapse rates are low. Dapsone is only slowly bacteriocidal and needs to be given daily. It is limited in its effectiveness and there is a high incidence of resistance if the drug is used alone. Side effects are rare but malaise, haemolytic anaemia and leucopoenia can occur. Rifampicin is a strongly bacteriocidal drug which is rapidly effective. Because of the slow rate of replication of *M. leprae* the drug need be given only once a month but resistance may occur on monotherapy. Clofazimine is weakly bacteriocidal but is highly effective in controlling lepromatous leprosy, particularly in suppressing the inflammation of erythema nodosum.

Patients with paucibacillary leprosy are generally treated with two drugs (rifampicin 600 mg/month and dapsone 100 mg/day) while those of multi-bacillary leprosy receive three drugs (rifampicin 600 mg/day, dapsone and clofazimine 50 mg/day and then 300 mg/month for 2 years). Treatment for paucibacillary leprosy requires 6 months while multi-bacillary leprosy should be maintained for at least a year and preferably two. However, all treated patients should be followed up for reactions or relapses for many years after completing treatment. The neuropathy is often treated with oral corticosteroids and 60% of patients are said to regain nerve function but this may take many months.

Immune-mediated (Lepra) reactions may develop in up to 30% of patients on treatment and may be associated with a slight shift towards lepromatous leprosy in previously untreated patients. There may be erythema nodosum, cropping of facial lesions and ocular involvement. Skin lesions may become erythematous, peripheral nerves painful and tender and sudden loss of function may occur. Patients should be treated with corticosteroids to control the serious effects of lepra reactions.

The social stigmas associated with deformity and scarring from leprosy remains a considerable worldwide problem despite extensive health education programmes run by WHO and other community projects. Leprosy control has been integrated into general health services in endemic areas increasing access to diagnostic and treatment facilities.

Diphtheria

Diphtheria is now extremely uncommon in developed countries as a consequence of immunity induced by mass immunization with diphtheria toxoid. However, sporadic cases still occur and there is a risk that a decline in population immunity may render the individual at greater risk given that immunization does not necessarily confer life-long immunity. Diphtheria is caused by infection with *Corynebacterium diphtheriae*, an aerobic Gram-positive organism which does not disseminate in deep tissues or blood but rather causes local mucosal necrosis with the formation of a thick 'pseudomembrane' of fibrin, epithelial cells, bacteria and neutrophils affecting the skin and the throat. The toxin may disseminate leading to myocarditis and neurological complications. The incubation period is 1–7 days (usually 2–4 days) and infection is generally manifest as inflammation or pseudomembrane formation over the pharynx or skin. Systemic involvement caused by dissemination of the toxin leads to neurological complications characterized by cranial nerve involvement and peripheral neuropathy.

Palatal and posterior pharyngeal wall paralysis commonly follows pseudomembrane formation and is associated with progressive cranial neuropathy leading to bulbar weakness manifest as dysarthria, dyphagia and aspiration; ocular involvement may also occur. A mixed sensorimotor demyelinating peripheral neuropathy develops later in the course of the disease, often many months after the onset. There is usually proximal weakness extending distally with severe paralysis and areflexia. Diaphragm and respiratory muscle weakness may develop requiring tracheal intubation and prolonged ventilation. Distal sensory impairment affects all modalities and autonomic involvement is common, manifest as sinus tachycardia, postural hypotension and urinary retention. The diagnosis is initially clinical and confirmed by throat swabs, membrane sampling for *C. diphtheriae* and toxin detection.

Management

Treatment involves the immediate administration of diphtheria antitoxin to neutralize circulating toxin, antibiotic treatment against *C. diphtheriae* (penicillin or erythromycin) and supportive management of cardiac, respiratory, bulbar and secondary infective complications. It is essential to recognize that immunity can wane and booster immunization should be offered every 10 years. Contacts are at considerable risk and throat swabs should be collected.

Botulism

Botulism is caused by a highly potent neurotoxin elaborated by *Clostridium botulinum*, an anaerobic Gram-positive rod which survives in the soil by forming spores. There are eight antigenically distinct strains of toxin (A–G) but each strain of *C. botulinum* produces only a single toxin. In human botulism, the toxin is absorbed from the gastrointestinal tract and haematogenously disseminated before the toxin either binds irreversibly to the presynaptic membrane of peripheral neuromuscular and autonomic nerve junctions to inhibit acetylcholine release. Recovery depends on the sprouting of new nerve terminals.

Forms of botulism

- Infantile;
- Food-borne;
- Wound;
- Iatrogenic;
- Inhalation (possible bioterrorism).

The mean incubation period of food-borne botulism is 2 days. The onset is with an acute gastrointestinal illness with neurological symptoms. Classically, patients develop non-specific gastrointestinal symptoms, a descending flaccid paralysis, cranial nerve symptoms, autonomic disturbance and ventilatory failure but they remain afebrile with normal sensation. Wound botulism has a longer incubation period but the symptoms and signs are similar to food-borne botulism. This condition occurs as a result of subcutaneous injection (skin popping) of black tar heroin that has become contaminated with *C. botulinum* when being cut or diluted prior to street sale.

Clinical presentation

Patients are apyrexial but may have nausea, vomiting, anorexia and abdominal pain. Cranial nerve deficits develop early including blurred vision, diplopia, dysarthria, dysphagia, dysphonia, facial weakness, ptosis and external ophthalmoplegia with mydriasis occurring because of accommodation paresis. There is flaccid limb weakness affecting the arms more than the legs and progressive respiratory impairment and arrest. Autonomic involvement is characterized by a dry mouth, unreactive pupils, paralytic ileus, gastric dilatation, bladder distension, orthostatic hypotension and constipation. There is an important differential diagnosis, which includes Guillain–Barré syndrome and myasthenia gravis, which is summarized in Table 8.13.

Table 8.13 Differential diagnosis of botulism.

Guillain–Barré syndrome and Fisher variant
Myasthenia gravis and myasthenic syndrome
Borrelia
Diphtheritic polyneuropathy
Tick bites
Curare poisoning
Poliomyelitis
Organophosphate poisoning
Nerve gases

Table 8.14 Management of botulism.

Supportive care	Patients should be admitted to ICU with close bulbar and respiratory monitoring Intubation and ventilation should be undertaken as necessary
Attempt to remove unabsorbed botulinum toxin	Controversial. In the absence of ileus and if ingestion is recent it is reasonable to induce catharsis or enemas
Antitoxin	Helpful particularly in type E botulism using the trivalent botulism antitoxin. This eliminates circulating toxin but does not remove botulinum toxin that has entered the neuromuscular junctions. The antitoxin therefore prevents worsening and should be administered as soon as possible, there is a risk of allergic reactions with equine antitoxins including urticaria and serum sickness
Wound treatment with débridement	Penicillin (care because lysing *Clostridium* botulism will release more toxin and potentially worsen the condition) Patients with wound infections should be treated with tetracyclines, metronidazole or chloramphenicol

Diagnosis

CSF and blood examination are normal. The *C. botulinum* may be isolated from the wound site, stool or food. The toxin is detected in serum, stool and food by bioassay using mice. The toxin is detected in two-thirds of food cases and 85% of wound botulism. Immunoassays to detect toxins in the stool and food are being developed but are not validated.

Neurophysiology

Nerve conduction studies are normal but repetitive stimulation shows a decremental response at low rates but an incremental response occurs at higher rates. Needle electromyography (EMG) confirms small polyphasic motor units and single fibre studies show jitter and block.

Management

The management of botulism is summarized in Table 8.14. The mortality of patients with food-borne botulism is approximately 10%, wound botulism 15% but the mortality for infant botulism is in the region of 5%.

Tetanus

Tetanus is rare in the UK but common worldwide and probably kills 500,000 adults per year.

Aetiology

Tetanus is caused by the neurotoxin tetanospasmin, elaborated by the anaerobic Gram-positive rod *Clostridium tetani*. This is a ubiquitous organism found in soil and faeces which persists as resilient spores capable of surviving many years and resistant to most disinfectants and boiling for up to 20 minutes. The spores germinate under appropriate anaerobic conditions. The toxin is produced in the wound and binds to peripheral motor nerve terminals before being transported via retrograde axonal transport into the spinal cord or brainstem, or both. The toxin ultimately migrates to the presynaptic terminals. It inhibits release of gamma-aminobutyric acid (GABA) and glycine, important inhibitory neurotransmitters. In the absence of the inhibitory influence of GABA and glycine, alpha motor neurones fire rapidly, producing rigidity. Preganglionic sympathetic neurones are also affected, resulting in increased catecholamine levels and sympathetic over-activity. Tetanospasmin can also produce weakness through blockade of acetylcholine release in a manner analogous to that of botulinum toxin.

Epidemiology

Tetanus occurs in neonates because of contamination of the umbilical stump. Children and adults may develop tetanus as a consequence of infected wounds, skin lacerations or as a consequence of intramuscular injections or drug abuse.

Clinical features

The incubation period varies from a few days to several weeks depending on the site of spore inoculation. There may be localized spasm and rigidity in the region of the wound. The onset may be with back pain, increased muscle tone and rigidity of the masseter muscles leading to trismus (lockjaw) and a similar rigidity of the facial muscles (risus sardonicus). There is a localized stiffness near to the injury with sustained rigidity of the axial muscles with involvement of the neck, back and abdomen and, in severe cases, reflex spasms and opisthotonus. Paroxysmal contractions of muscles appear in response to slight stimuli, and in severe cases are bad enough to cause limb fractures, tendon avulsion and rhabdomyolysis. Spasms of respiratory muscles lead to asphyxia, vocal cord obstruction and aspiration associated with increased bronchial secretions, hypersalivation and dysphagia.

Autonomic manifestations are common in severe tetanus with profuse sweating, hypersalivation and extreme hyperpyrexia. Fluctuations of blood pressure and heart rate are cardinal features and these may be followed by arrhythmias and circulatory failure. There may be transient glycosuria. There is also excessive bronchial secretion, gastric stasis, diarrhoea, acute renal failure and volume depletion.

Diagnosis

The diagnosis is made on the basis of history of the spasms and examination although the finding of *Clostridium tetani* in a wound guides the diagnosis.

Table 8.15 The management of tetanus.

Eradication of the causative bacterium	Debridement of the wound Antibiotics (metronidazole 500 mg q.i.d. for 7–10 days)
Neutralize any unbound toxin	Equine or human antitoxin are used but human immunoglobulin (100–300 mg IU/kg i.m.) is preferred because there is less anaphylaxis
Supportive therapy during the acute phase	Nursing in a calm, quiet environment with cardiorespiratory monitoring Fluid balance, nutrition and the control of muscle spasms with diazepam, midazolam Neuromuscular blockade with vecuronium
Vaccination	Primary childhood immunization programmes as five doses of combined DPT in the UK given at 2 months, 4 months, 6 months, 3–5 years and 13–18 years. Boosters are recommended every 10 years
Post injury wound care	Wounds associated with tissue necrosis infection or retained foreign bodies are important precipitant factors

DPT, diptheria, pertussis and tetanus.

Differential diagnosis

Strychnine is a competitive antagonist for glycine. Intake with poisoning is characterized by spasm and rigidity in the abdominal muscles. Dystonic drug reactions may also mimic the stiffness and involuntary truncal spasms of tetanus. Non-organic disorders may also be mistaken for tetanus.

Treatment

Treatment in the ICU has resulted in a marked improvement in prognosis for patients with tetanus but the mortality is still approximately 10%. Severe muscular rigidity may last for weeks, with assisted ventilation being required for up to 3–4 weeks. Complete recovery is typical, although mild painful spasms can persist for months. Management is summarized in Table 8.15.

Infective endocarditis

Infective endocarditis is caused by direct bacterial colonization of the endothelial surface of the heart, usually on the valves. Endocarditis affecting a native valve is usually associated with congenital, rheumatic or degenerative valve disease but occurs commonly in intravenous drug abusers. Endocarditis develops on prosthetic valves in up to 6% of cases over 5 years. Approximately 30% of patients with endocarditis have neurological complications and often these may be the presenting features. Most cases of native valve endocarditis are caused by *Strep. viridans*, *Strep. bovis* or *Staphylococcal aureus* with the latter being much more common in endocarditis amongst intravenous drug abusers in whom the right-sided valves are more often affected.

Clinical presentation is characterized by fever, systemic symptoms including weight loss and anorexia, new or changing heart murmurs or peripheral vasculitic signs including petechiae, splinter haemorrhages or Osler nodes. Neurological complications are common and brought about either by bacteraemia leading to meningitis, cerebritis or a parameningeal focus or by recurrent emboli which may be infective. Cerebral emboli commonly involve the anterior circulation and are frequently multiple with up to 10% being haemorrhagic. There is often a preceding transient ischaemic attack and concurrent systemic emboli are common. Septic emboli may cause cerebral infarction, meningitis or parenchymal abscess but they also lead to the development of mycotic aneurysms which occur when an infected arterial wall becomes weakened (Figure 8.6). They usually develop in distal arterial vessels and may also occur as a result of direct local spread. Mycotic aneurysms carry a high risk of rupture into the parenchyma and subarachnoid space leading to focal neurological deficits, meningism, declining consciousness and coma. Cerebral abscesses may be multiple and also lead to severe focal or generalized neurological deficits. Bacterial meningitis is common in endocarditis and carries a poor prognosis if severe. It may

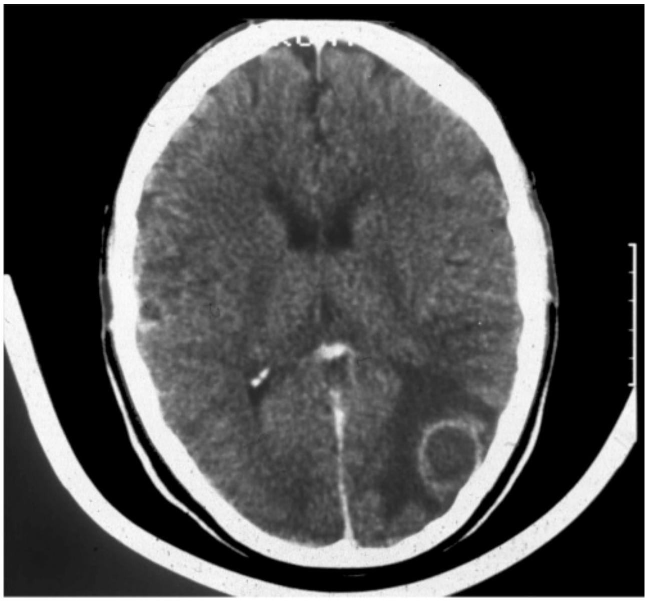


Figure 8.6 Mycotic aneurysm in *Streptococcus viridans* endocarditis (CT enhanced).

contribute to the development of cerebral vasculitis particularly in staphylococcal disease. Ocular involvement occurs rarely and is caused by involvement of the retinal vasculature, optic or cranial nerves or brainstem and may lead to central retinal artery occlusion, ophthalmoplegia or field loss.

The diagnosis should be considered in any patient with a focal or generalized neurological deficit and unexplained pyrexia. The diagnosis of endocarditis depends on appropriate cardiac imaging including transthoracic and transoesophageal echocardiography, investigation of neurological involvement includes serial blood cultures, urine microscopy for red cells, CT scan, magnetic resonance angiography (MRA) and CSF examination.

Treatment involves the urgent initiation of organism-specific antibiotics and depends on bacterial sensitivities and the underlying risk factors. Native valve *Strep. viridans* endocarditis is treated with benzylpenicillin (or ceftriaxone) and gentamicin in regimens varying 2–6 weeks depending on penicillin resistance. Longer courses are given for prosthetic valve *Strep. viridans* endocarditis and vancomycin is used if there is penicillin allergy. Native valve staphylococcal endocarditis requires a 6-week course of flucloxacillin or, if there is methicillin-resistant *Staph. aureus*, vancomycin is used. Prosthetic valve staphylococcal endocarditis usually requires the addition of gentamicin to flucloxacillin or vancomycin. The management of cerebral emboli and mycotic aneurysms is difficult. Anticoagulation should be avoided because of the high risk of haemorrhagic transformation. Neurosurgical intervention is rarely indicated and a conservative approach is usually justified depending on the size and location of the aneurysm. Despite advances in antibiotic management and supportive care, the prognosis of endocarditis once there is neurological involvement is poor, with mortality of 30–80%.

Viral disease of the nervous system

Viruses can cause a variety of diseases in the CNS. The most important are viral meningitis, encephalitis and encephalomyelitis.

Viral meningitis

Viruses causes an isolated aseptic meningitis characterized by symptoms and signs of meningeal irritation with a CSF pleocytosis in the absence of bacterial, fungal or parasitic infection. There is no parenchymatous brain or spinal cord inflammation. However, in most cases there is mixed meningo-encephalitic or encephalomyelitic involvement.

Aetiology

Non-polio enteroviruses are by far the most common cause of viral meningitis, these include coxsackie and echovirus strains. The main causes include:

- Enterovirus:
- Echovirus;
- Coxsackie A, B;
- Enterovirus 70, 71;
- Mumps;
- Measles;
- Herpes simple virus 2 (HSV-2);
- Varicella zoster virus (VZV);
- Epstein–Barr virus (EBV);
- Cytomegalovirus (CMV);
- Human herpes virus 6 (HHV-6);
- Arboviruses;
- HIV;
- Adenovirus;
- West Nile virus.

Viral meningitis is a relatively uncommon complication of systemic viral infection. Most viruses gain access to the body from the oropharynx. They are amplified (multiply) in lymphatic tissue, spread to the bloodstream (viraemia) and cross the choroid plexus or capillary endothelial cells to reach the CNS. Rarely, viruses may enter the CNS by direct transmission through axons.

Clinical features

In viral meningitis there may be a flu-like prodrome followed by the sudden onset of intense frontal headache, fever and neck stiffness associated with photophobia, malaise, myalgia and severe nausea and vomiting. Although there is pyrexia, neck stiffness and meningeal signs, patients are generally less unwell than those with bacterial meningitis. A pruritic rash, pleurodynia or myocarditis may be present. There is a wide differential diagnosis of aseptic meningitis which is summarized in Table 8.16.

Diagnosis

The peripheral white cell count is usually normal but may be increased or decreased and liver function may be abnormal. The CSF is clear and colourless with a normal to moderately elevated pressure, the cell count may be up to 1000 cells/mm^3, it is usually <300 and mononuclear lymphocytes predominate, although polymorpholeucocytes may be present, glucose is usually normal but may be slightly depressed and the protein is normal or mildly elevated.

Viral isolation

Viral isolation is undertaken from the throat, urine or stool and antibody studies are possible in serum or CSF. The detection of viral RNA or DNA is now undertaken using PCR in the serum or CSF. The prognosis in viral meningitis is good with spontaneous recovery usually occurring within 1–2 weeks. However, there may be residual deficits in up to 5% including malaise, fatigue, mild intellectual and language difficulties, seizures, isolated cranial nerve lesions and optic neuritis.

Management

The treatment is supportive care but it is necessary to admit the patient if there is a possibility of bacterial meningitis. Herpes virus meningitis can be treated with a variety of antiviral agents including aciclovir, famciclovir, valaciclovir, ganciclovir and

Table 8.16 Differential diagnosis of aseptic meningitis.

Infections
Viruses
Viral meningitis
Bacterial
Partially treated bacterial meningitis
Brucellosis
Listeria
Mycoplasma pneumoniae
Spirochete infection (syphilis, leptospirosis, *Borrelia*)
Mycobacterium (tuberculosis)
Whipple's disease
Endocarditis
Parameningeal infection – abscess, empyema, osteomyelitis, sinusitis
Rickettsial infection
Fungi
Parasites
Vasculitis
Inflammation
Sarcoid, Behçet's disease
Collagen vascular
SLE, RA, polyarteritis nodosa, mixed connective tissue disease, Sjögren, Wegener, lymphomatoid granulomatosis
Meningeal carcinomatosis
Leukaemia/lymphoma
Chemical meningitis
Contrast materials
Drugs
Non-steroidal anti-inflammatory drugs
Antineoplastic drugs
Immunosuppressants – azathioprine
Antibiotics – septrin, sulfasalazine, ciprofloxacin, amoxicillin
Intravenous immunoglobulin
Valaciclovir

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

foscarnet. The only therapy of clinical use for enterovirus meningitis is immune serum globulin, but the new antipicorna viral agent pleconaril may have an important role.

Chronic and recurrent meningitis

Meningitis may be recurrent either because the patient is predisposed to repeated bacterial infection, recurrent non-purulent infection or because of a non-infective aetiology. Chronic meningitis may be defined as meningitis that persists for 4 weeks or more without showing any recovery. The condition often presents with a more encephalitic-like picture of progressive impairment of cognition and consciousness following a fluctuating course. Any of the conditions listed in Table 8.17 may cause a chronic meningitis or recurrent meningitis:

Table 8.17 Causes of chronic or recurrent meningitis.

Continuing sepsis, potential access to CNS (e.g. skull base or middle ear defect) or immunosuppression (e.g. hypogammaglobulinaemia).
Chronic meningeal infection
Brucella
Syphilis
Borrelia
Fungi
Cryptococcus
Coccidiodomycosis
Histoplasmosis
Blastomycosis
HIV
Parameningeal infection
Periodic reactivation of latent infection
HSV
VZV
EBV
CMV
Toxoplasmosis
Immunosuppression
Antibody deficiency
Complement deficiency
Splenic dysfunction
Inflammatory disorders
Vasculitis
Collagen vascular disease
Sarcoidosis
Behçet's disease
Vogt–Koyanagi–Harada syndrome
Migraine with pleocytosis
Medication
Non-steroidal anti-inflammatory drugs
Antineoplastic drugs
Immunosuppressants – azathioprine
Antibiotics – septrin, sulfasalszine, ciprofloxacin, amoxicillin, IVIG
Valaciclovir
Antiepileptic medication – lamotrigine, carbamazepine
Lymphoma
Immune reconstitution in highly active retroviral treatment in AIDS
Chemical meningitis
Mollaret's meningitis

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HSV, herpes simples virus; IVIG, intravenous immunoglobulin; VZV, varicella zoster virus.

Mollaret's meningitis

This is a rare condition in which recurrent episodes of pyrexia and meningism occur but may be separated by asymptomatic periods lasting days, weeks or months. The attacks resolve spontaneously with no residual deficit and they usually cease within a few years. During attacks the CSF shows a mild elevation in the protein and pleocytosis with characteristic monocytic cells. HSV types 1 and 2 have been isolated from the CSF.

Encephalitis

Encephalitis is acute infection of the parenchyma of the brain, usually caused by a virus, which results in a diffuse inflammatory process, often also involving the meninges. Most common viral infections can rarely lead to viral encephalitis. Encephalitis causes focal or multi-focal neurological deficits or seizure activity. Acute disseminated encephalomyelitis (Chapter 10) may occur as an immunologically mediated para-infectious phenomenon following a variety of infections or after vaccination.

Within the UK and North America, after the neonatal period, the most common severe forms of infectious encephalitis are those caused by:

- HSV-1;
- VZV;
- EBV;
- CMV;
- HHV 6 and 7;
- Enteroviruses;
- Adenoviruses;
- Influenza virus A and B;
- Arboviruses;
- *Mycoplasma pneumoniae*;
- HIV seroconversion.

Pathophysiology

There are several mechanisms by which viruses can cause encephalitis. Organisms that cause encephalitis require the ability to infect brain tissue (neurotropism) but not necessarily the ability to infect neurones (neuronotropism).They usually enter the CNS via direct haematogenous dissemination but may affect the brain via retrograde neuronal spread. Arbovirus encephalitides are zoonoses in which the virus life cycle takes place both in the biting arthropod and an invertebrate host. The virus is then transmitted by an insect bite and undergoes local replication in the skin before spreading to the brain and causing human encephalitis. Pathological examination shows involvement of the grey matter with perivascular inflammation, neural destruction, neuronophagia and tissue necrosis.

Incidence

In the USA, the annual incidence of viral encephalitis is between 3.5 and 7.4/100,000 of the population. In the UK, the reported incidence is lower. HSV is the most frequent cause but VZV, enterovirus and influenza A are also common. There remains considerable geographical variation and arbovirus encephalitis is common in the Americas and Asia.

Clinical features

The clinical manifestations of encephalitis are often most severe in infants and those over the age of 65. It is characterized by fever in 90% of patients. Seizures are common and help to distinguish acute infective encephalitis from acute disseminated encephalomyelitis. The presence of headache, pyrexia and meningism suggest leptomeningeal irritation while parenchymatous involvement leads to focal neurological signs including seizures and alteration of consciousness progressing to stupor and coma. More commonly, behavioural and speech disturbances develop and abnormal movements are associated with lesions in the basal ganglia and pituitary, involvement of the hypothalamus may cause hypothermia.

Diagnosis

In assessing a patient with suspected viral encephalitis it is essential to take a detailed history of travel and it is also important to note the season of onset, any contact with animals and any evidence of immunosuppression. CSF examination should be undertaken if possible. MRI appearances may be characteristic in herpes simplex encephalitis (see below) but are non-specific in other causes.

Herpes simplex encephalitis

The majority of cases of herpes simplex encephalitis (HSE) in adults are caused by HSV-1. Ten per cent are caused by HSV-2, usually associated with immuno-compromise or occurring in the neonate. Primary infection usually develops in the oropharyngeal mucosa before the virus is transported by retrograde transneuronal spread via the trigeminal nerve to establish latency in the olfactory bulb or trigeminal ganglion. Molecular analysis of paired oral and brain sites have indicated HSE can occur as the result of a primary infection, a reactivation of latent HSV in the trigeminal ganglion or reinfection by a second HSV. However, the presence of labial herpes has no diagnostic specificity to HSE. The herpes virus leads to inflammation, infection and necrotizing lesions particularly in the inferior and mesial temporal lobes which may also involve the orbital frontal cortex and limbic structures.

The onset of HSE is with fever, headache and alteration of consciousness which may develop gradually or rapidly over a matter of hours. The most common manifestations are personality change, dysphasia with progressive behavioural disturbance and occasional psychotic features. Less typical features include the development of hemiparesis or a visual field defect (particularly superior quadrantic). Focal or generalized seizures are often associated with olfactory or gustatory hallucinations.

Investigation

The MRI characteristically shows high signal areas of unilateral focal oedema on T2 images in the medial and inferior temporal

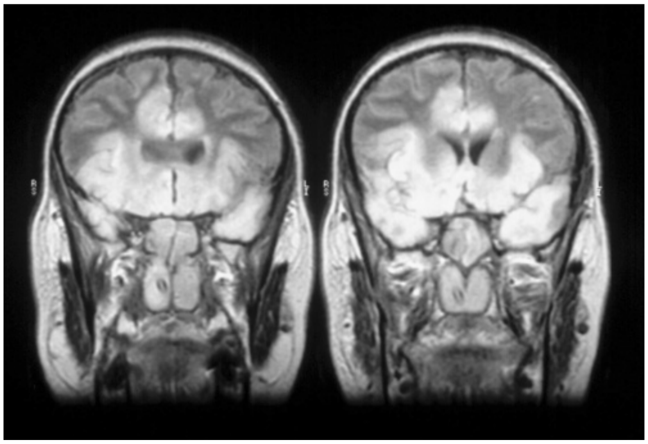


Figure 8.7 Fulminant herpes simplex encephalitis; extensive temporal lobe and diffuse parenchymal inflammation (MRI T2W).

lobes, extending into the insular cortex and frontal lobe; the changes may be extensive and midline shift may be present if there is significant vasogenic oedema (Figure 8.7).

The electroencephalogram (EEG) is characterized by periodic stereotyped, lateralized sharp and slow wave complexes occurring at regular intervals between 2 and 3 seconds. CSF is generally under an increased opening pressure and may show a mild to moderate lymphocytic pleocytosis of 5–500/mm³; there may be a mild to moderate elevation in the protein (0.6–6 g/L) and a normal or mildly decreased glucose. In approximately 5% of patients CSF examination is normal. PCR examination of the CSF is sensitive and specific for the detection of HSV DNA. It should be positive after about 5 days of infection but clears again after 14 days of illness. PCR may also be used to guide the duration of treatment with aciclovir. PCR has also become increasingly valuable in the diagnosis of virus encephalitides from other causes such as CMV, VZV, influenza and enterovirus. Brain biopsy is now rarely undertaken but may be considered if diagnostic uncertainty remains.

Management

High-dose intravenous aciclovir (10–15 mg/kg body weight 8 hourly) reduces the mortality of HSE from 70% to 20%. It is also appropriate treatment for VZV-related CNS disease. In initial studies, treatment was continued for 10 days but it is now conventional to treat for 14–21 days or at least until the PCR has become negative. Occasionally, HSV may be resistant to aciclovir and foscarnet is indicated in this situation. Patients with HSE can develop seizures, which require specific treatment; corticosteroids may be of value if cerebral oedema develops and, occasionally, intracranial pressure monitoring and even surgical decompression may be necessary. Although high-dose aciclovir has reduced mortality from HSE, there is still a significant morbidity that may occur including severe memory impairment (up to 69%), personality behavioural changes (up to 45%), epilepsy (up to 25%) and dysphasia (up to 4%). Early treatment is essential for the reduction of morbidity, particularly before the development of impairment of consciousness.

Other causes of encephalitis

Other causes of encephalitis are summarized in Tables 8.18 and 8.19.

Varicella zoster virus

VZV is a large herpes virus. Primary infection causes chickenpox and secondary reactivation leads to dermatomal shingles or disseminated herpes zoster. Chickenpox (varicella) is a usually self-limiting exanthematous disorder which may be associated with pneumonitis or secondary bacterial infection. Neurological complications include a severe encephalitis, meningitis, myelitis and cerebellar ataxia. Rarely, an acute toxic encephalopathy or Reye syndrome may occur. In the elderly there is a high risk that post-herpetic neuralgia may develop, after the rash of shingles resolves. Involvement of the geniculate ganglion leads to ear pain, facial nerve palsy and herpetic lesions in the external auditory meatus (Ramsay-Hunt syndrome). Disseminated herpes zoster occurs particularly in the immunosuppressed. Herpes zoster may also be complicated by the development of a vasculopathy affecting both small and large vessels causing infarction. VZV may also cause encephalitis, myelitis, radiculopathy or a cranial neuropathy including optic neuritis. In VZV large vessel angiitis, steroids should be administered with aciclovir and the benefit of prolonged high-dose valaciclovir following aciclovir is currently being studied.

Cytomegalovirus

CMV is a ubiquitous herpes virus that only affects humans. The virus often persists in the throat following infection and may become latent for many years. Infection is usually transient and asymptomatic but it may cause cytomegalic inclusion disease in the newborn and neurological disease in the immuocompromised adult, particularly following organ transplant or in AIDS. In HIV-positive patients the most common complications are lumbo-sacral polyradiculopathy and retinopathy. Other forms of peripheral neuropathy may occur and encephalitis and myelitis are also associated with CMV.

Epstein–Barr virus

EBV is a lymphotropic herpes virus which, like all herpes viruses, may establish latency before being reactivated. It replicates in B cells, causes infectious mononucleosis and is associated with lymphoproliferative disorders – Burkitt and Hodgkin lymphoma, hairy cell leukaemia, lymphocytic lymphoma and nasopharyngeal carcinoma. Neurological complications include aseptic meningitis, encephalitis, acute cerebellar ataxia, cerebritis, transverse myelitis, polyneuropathy (including Guillain–Barré), mononeuropathy (including brachial plexopathy) and cranial nerve palsies (especially facial nerve). These may occur as a consequence of

Table 8.18 Viruses that may infect the CNS (excluding arboviruses).

Family of virus	Virus		
Herpes	HSV-1		
	HSV-2		
	VZV		
	CMV		
	EBV		
	HHV-6		Linked with meningoencephalitis, GBS and retinitis
			Occasionally found in CSF of patients with AIDS but significance unknown
Orthomyxovirus	Influenza		May present as a frontal lobe or limbic syndrome without disturbance of consciousness
			Guillain–Barré-like neuropathy, myelitis
	Avian flu A (H5N1)		Characterized by diarrhoea, seizures and progression to severe encephalopathy leading to coma and death
			CSF protein is elevated
Picornavirus	Enterovirus (non-polio)		Enterovirus infection is usually asymptomatic or manifest as an erythematous or maculopapular rash
	Coxsackie Echo		Usually associated with a good prognosis but enterovirus 71 may present with herpangina, hand, foot and mouth disease, myoclonus, tremor and cranial nerve involvement
	Polio		May be complicated by acute flaccid paralysis or long-standing chronic meningo-encephalitis particularly in the young or patients who are immunosuppressed
			Enterovirus can be isolated from CSF faecal, throat and serum specimens
Paramyxoviruses	Mumps	Worldwide (Winter & Spring)	Usually starts several days after parotitis and usually resolves without sequelae except for occasional hydrocephalus due to ependymal cell involvement
	Measles	Worldwide (Winter & Spring)	Rash, myelitis, encephalitis
	Nipah virus	Asia (All year)	Rare. Contracted from pigs
			Presents with encephalitis and focal cerebellar or brainstem signs
		Direct transmission	Segmental myoclonus and systemic involvement, characterized by hypertension and tachycardia
			Encephalitis may be delayed for several months after exposure to the virus
			MRI shows increased signal in cortical white matter
Arenavirus	Lassa fever	Africa	
	Lymphocytic-choriomeningitis	Europe, America, Australia, Japan (usually winter)	
	Rabies		See text

CMV, cytomegalovirus; CSF, cerebrospinal fluid; EBV, Epstein–Barr virus; HHV, human herpes virus; HSV, herpes simple virus; MRI, magnetic resonance imaging; VZV, varicella zoster virus.

direct viral infection or as a parainfectious phenomenon. EBV causes <5% of viral encephalitis and is associated with impaired level of consciousness, seizures and focal deficits. Although recovery is usual, permanent deficit may occur with residual chorea and cognitive impairment.

Arboviruses (arthropod-borne viruses) (Table 8.19)
Specific arboviruses can be predicted on the basis of geographical location and the demographic pattern of infection. Subacute inoculation by mosquito or tick vector is followed by local tissue and lymph node replication, viraemia and finally invasion of deep soft tissues, organs and CNS. Arbovirus encephalitis predominantly affects cortical grey matter but it may also involve the brainstem and thalamic nuclei. Arboviruses can occasionally cause meningitis or meningo-encephalitis.

Rickettsial disease

Rocky Mountain spotted fever (RMSF) is caused by a minute polar staining bacillus that occurs in freshly laid eggs of infected ticks. A minimum of 6 hours attachment of the tick to the skin surface is required before the *Rickettsia* are transmitted. There is subsequent invasion and multiplication within endothelial smooth muscle cells leading to the development of a vasculitis. Severe RSMF is associated with encephalitis and systemic signs including purpura, hypovolaemia, hypotension, prerenal failure and cerebral and pulmonary oedema. Other rickettsial infections develop over 10–14 days and tend to be slightly less severe but are also associated with a purpuric rash and encephalitis. Treatment with doxycycline is given until the patient has been

Table 8.19 Arboviruses that may infect the CNS.

Alphavirus	Eastern Equine	Eastern & Gulf USA (Summer)	Severe, rapidly progressive, virulent encephalitis that affects children High mortality rate (<35%)
	Western Equine	Western USA (Summer)	Encephalitis, predominantly affects children Mortality rate <10%
	Venezuelan	South and Central America (Rainy season)	Occurs in large outbreaks but usually self-limiting and encephalitis is rare but neurological sequelae in <20%
Flavivirus	St Louis	USA (Summer)	Most common vector transmitted cause of aseptic meningitis in the USA Aseptic meningitis accounts for approximately 15% of all symptomatic cases Often asymptomatic and characterized by a mild febrile illness but severe encephalitic illness can occur in the older age group when mortality may rise to 20% Sequelae occur in 10% including memory loss chronic fatigue, sleep disturbance, headaches and occasional seizures Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
	Japanese	Asia (Summer) Transmitted by mosquito bite	Affects children and young adults, most common arbovirus worldwide Non-specific prodrome but seizures are common. In adults, extrapyramidal involvement may occur with a transient parkinsonian-like syndrome, tremor, choreoathetotic head nodding or axial ridigidy and flaccid paralysis may occur due to damage of anterior horn cell Occasionally, JVE may present as a severe fulminant encephalitis characterized by fever, vomiting, convulsion and impaired consciousness leading to coma Mortality <50% with a high incidence of residual neurological sequelae MRI shows lesions in basal ganglia and thalamus Diagnosis by ELISA or PCR of serum and CSF or postmortem brain tissue Vaccination is possible with 3 doses of inactivated JVE
	West Nile	Africa, Asia Middle East (Summer) Transmitted by mosquito bite	Usually aymptomatic. May develop with a flu-like illness with incubation period of 3–15 days. Rash, arthralgia, hepatosplenomegaly and pancreatitis Neurological involvement in <15% – encephalitis, encephalomyelitis, aseptic meningitis or the development of an axonal or demyelinating polyneuropathy (resembling Guillain–Barre syndrome) Mortality ranges 12–14% – may be a residual flaccid weakness resembling poliomyelitis
	Far East	Eastern Russia (Summer)	Associated with partal epilepsy and high mortality (<20%)
	Central European	Central Europe	Tick-borne Flaccid proximal weakness
	Powessan	Canada (Summer & Autumn)	Tick-borne Severe encephalitis Residual cognitive impairment common High mortality
	Dengue	Tropics (SE Asia & Indian subcontinent)	Presents with severe influenza like illness or haemorrhagic fever Headaches, arthralgia and myalgia Less commonly this can give rise to encephalitis or encephalopathy and rarely transverse myelitis or polyneuropathy resembling Guillain–Barré syndrome Haemorrhagic form also causes intracerebral haemorrhage, hepatic failure and Reye syndrome-like illness Low risk of sequaelae and low mortality
	Murray Valley	Australia Mosquito borne	
	Kunijin	Australia	
	Rocio	Brazil	
	Russia	Russia Tick-borne	In cooler northern climates, flaviviruses transmitted by ticks rather than mosquito
Bunyavirus	La Crosse	Central USA	Predominantly a viral encephalitis of children which tends to be mild and self-limiting with a low mortality
Filovirus	Ebola	Africa	
	Marburg	Africa	

CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; JVE, Japanese virus encephalitis; PCR, polymerase chain reaction.

afebrile for >2 days. Tetracycline and chloramphenicol are alternatives.

Polio and the post-polio syndrome

Despite a global policy aimed at eradication, pockets of wild polio still exist and there is a small incidence of vaccine-induced polio in infants and adults. Present policies are directed towards mopping up residual sources with the eventual discontinuation of routine immunization. Acute poliomyelitis is rarely encountered in the UK following its successful eradication; however, 'imported' poliomyelitis still occurs and it is necessary to distinguish acute poliomyelitis from other causes of acute flaccid paralysis (Table 8.20).

Poliomyelitis is caused by an enterovirus of high infectivity whose main route of infection is via the human gastrointestinal tract. There are three subtypes but, before the introduction of polio vaccine, type I accounted for 85% of paralytic disease. Epidemics of polio occurred, most commonly, during the summer months, in the temperate climates of the northern hemisphere and the incidence was greatest where children bathed together.

The incubation period is 7–14 days. The acute illness is characterized by minor flu-like symptoms, followed by a meningitic phase as the virus reaches the CNS. The onset of spinal poliomyelitis is associated with myalgia and severe muscle spasms and the subsequent development of an asymmetrical, predominantly lower limb, flaccid weakness which becomes maximal after 48 hours. A purely bulbar form, with minimal limb involvement, also occurs carrying a particularly high mortality rate because of vasomotor disturbances such as hypertension, hypotension and circulatory collapse, autonomic dysfunction, dysphagia, dysphonia and respiratory failure. Polio may also cause an acute encephalitis. Recovery from the acute infection can be slow and prolonged periods of rehabilitation are necessary for recovery of limb function, severe permanent impairment is common.

The virus is commonly isolated from the nasopharynx or the stool. In the absence of a viral isolate, serological diagnosis can be established by neutralization of sera against paired antigens of the three serotypes. PCR is now the technique of choice for serotypic identification of poliovirus and for differentiation of wild and vaccine-strain poliomyelitis.

Differential diagnosis (Table 8.20)

Acute flaccid paralysis is associated with infection by other enteroviruses including coxsackie virus A7 and enterovirus 71, tick-borne encephalitis and by flaviviruses including Japanese encephalitis and, more recently, West Nile virus. The differential diagnosis of asymmetric motor flaccid paralysis includes, Guillain–Barré syndrome, acute intermittent porphyria, HIV neuropathy, diphtheria and *Borrelia burgdorferi* (Lyme disease) infections.

Table 8.20 Causes of acute flaccid paralysis.

Infection
- Viral
  - Enterovirus
    - Poliomyelitis (wild and vaccine associated)
    - Enterovirus 71, Coxsackie A
  - Flavivirus
    - Japanese encephalitis
    - West Nile encephalitis
  - Herpes virus
    - CMV
    - EBV
    - VZV
  - Tick-borne encephalitis
    - HIV-related (associated with opportunistic infections)
    - Other neurotropic viruses (e.g. rabies)
- Borrelia
- Mycoplasma
- Diphtheria
- Botulism

Neuropathy
- Acute inflammatory polyneuropathy
- Acute motor axonal neuropathy
- Critical illness neuropathy
- Lead poisoning
- Other heavy metals
- Porphyria
- Hyperkalaemia

Spinal cord
- Acute transverse myelitis
- Acute spinal cord compression
- Trauma
- Infarction

Neuromuscular junction
- Myasthenia gravis

Muscle
- Polymyositis
- Viral myositis
- Post-infectious myositis
- Critical illness myopathy

Non-organic

CMV, cytomegalovirus; EBV, Epstein–Barr virus; VZV, varicella zoster virus.

Prevention

Salk trivalent inactivated polio vaccine (IPV), introduced in 1956, is administered by injection and stimulates serum IgM, IgG and IgA, but not secretory IgA, immunity being induced by antibody transuding into the oropharynx. Sabin trivalent oral live attenuated polio vaccine (OPV) replaced the Salk vaccine in 1962; this is composed of live attenuated strains of polioviruses I, II and III grown in cell culture. The advantages over the Salk vaccine are that it is cheap; can be administered orally; and causes an active attenuated infection of the oropharynx and intestinal endothelium stimulating local secretary IgA in addition to serum antibody production. Furthermore, the attenuated virus is excreted in the faeces leading to herd immunity. Complete immunization with OPV has, conventionally, included four doses routinely given at 2, 4 and 6–18 months, with a booster at 4–6 years.

Post-polio syndrome

Many patients with residual impairments following previous paralytic poliomyelitis develop new disabilities after a period of prolonged stability. These late changes include progressive muscular atrophy, weakness, pain and fatigue but most patients are aware of late functional deterioration manifest as impairment of activities of daily living, mobility, upper limb function and respiratory capacity. The new wasting and weakness is probably caused by distal degeneration of post-poliomyelitis motor units associated with age, overuse or disuse. Thus, new impairments often occur as a consequence of prolonged stresses on skeletal deformity and previously weakened muscles. The extent of the original limb, trunk, respiratory and bulbar weakness is an important factor in predisposing to the development of late functional deterioration. Although there are no adequate longitudinal studies, experience suggests that post-polio functional deterioration is not necessarily an ongoing process. Fatigue and reduced mobility, often may progress slowly or stabilize. The prognosis also depends on the nature of any underlying cause for the functional deterioration.

Subacute sclerosing panencephalitis

Subacute sclerosing panencephalitis is a progressive neurological condition associated with measles occurring at a young age (usually <2 years). The onset is usually in childhood at an average of 6–8 years, with a male : female ratio of 3 : 1 but the condition can occur in adults and can be triggered during pregnancy. The clinical course is highly variable but the onset is usually with behavioural and intellectual change developing over weeks or months. There is frequently a decline in school performance with withdrawal, hyperactivity and aggressive behaviours often with emotional lability. Motor signs progressively develop with dysarthria, incoordination and tremor. There is usually a progressive decline with periodic stereotyped attacks of myoclonic jerks and seizures. Higher functions deteriorate with worsening apraxia, visuo-spatial abnormalities and progressive language impairment. Profound disability is associated with choreathetosis, dystonia, persistent myoclonic jerking and autonomic instability with hyper-pyrexia, tachycardia and an abnormal respiratory pattern. There may be an associated choroido-retinitis pigmentosa and optic atrophy. The condition usually progresses over 1–3 years and 10% may survive for up to 10 years but a fulminate course with death in 3 months is seen in about 10% of patients. The condition is associated with early infection by measles virus which is an enveloped RNA virus and can be recovered from the CSF and brain in most patients. The diagnosis is based on the clinical pattern and characteristic bilateral synchronous and symmetrical periodic discharges occurring every 4–12 seconds on the EEG. There is also an associated slower background activity which becomes disorganized. An elevated measles virus antibody is found in serum and CSF. MRI shows focal or generalized high white matter lesions in frontal, temporal and occipital regions. There is no effective treatment.

Rabies

Rabies is a zoonosis of certain mammals endemic in all continents, it is caused by a lyssa virus which is inoculated into the tissue of a wound usually caused by a canine (usually dog) or bat bite. It may replicate locally in muscle cells or attach directly to nerve endings. It then enters the presynaptic nerve terminal and is carried in a retrograde direction. On reaching the CNS there is massive viral replication in neurones before transynaptic transmission of the virus occurs from cell to cell. Viral proteins accumulate in the cytoplasm appearing as inclusions (Negri bodies).

Clinical features

Clinical features develop up to 1–3 months after the bite. The onset is with a prodrome of fever, nausea, vomiting, chills, malaise, fatigue, insomnia and worsening encephalopathy before the development of pain, pruritus, paraesthesiae and fasciculation close to the bite site. Patients may develop furious rabies (80%) or paralytic rabies (20%).

Furious rabies is characterized by episodes of excitement and hyper-excitability fluctuating with periods of lucidity. Aggressive behaviour, confusion and hallucinations develop. Autonomic dysfunction is manifest as hypersalivation, sweating and piloerection. Patients develop severe muscle spasms of the throat, trunk and respiratory muscles triggered by the sight or sound or attempts to drink water (hydrophobia) or even by air (aerophobia). The spasms cause generalized extension, convulsions and opisthotonus with death usually occurring within 1 week of the onset of furious rabies as a consequence of cardiac arrhythmias, myocarditis and respiratory arrest. Paralytic rabies is less common than furious rabies and it may occur following vampire bat transmission; in patients who have been affected by attenuated virus; or following post-exposure vaccination. It is associated with an ascending paralysis leading to constipation, urinary retention, respiratory failure and an inability to swallow. Flaccid muscle weakness develops early in the course of the disease. Hydrophobic spasms may also occur and patients may go on to develop bulbar and respiratory muscle involvement but survive longer than classic furious rabies.

The differential diagnosis includes viral encephalitis, tetanus, post-vaccinal encephalomyelitis and Guillain–Barré syndrome.

Diagnosis

A CSF mononuclear pleocytosis develops, usually within the first week, but serum neutralizing antibodies are not present until the tenth day of the illness. Viral isolation is occasionally possible from saliva, throat, trachea, CSF or brain biopsy and skin biopsy and immunofluorescent antibody techniques will demonstrate an antigen in the small nerves of the skin taken from the nape of the neck, often in a hair follicle. PCR detection of rabies virus RNA has also been demonstrated from the brain, saliva and CSF. Post-mortem virus isolation and brain cultures should be taken if possible.

Management

Management is supportive. Patients with acute rabies are treated with heavy sedation and adequate analgesia to relieve terror or pain. Acute interventional care may be necessary to manage cardiac arrhythmias, cardiac and respiratory failure, raised intracranial pressure, convulsions and fluid and electrolyte disturbances but only occasional reports of survival have been documented, usually in patients who had received rabies vaccine before the onset of symptoms. Vaccination before exposure is strongly recommended to travellers as it provides protection after unrecognized exposure and may simplify treatment. Post-exposure treatment is summarized in Table 8.21.

Prevention is achieved with careful attempts to eradicate rabies from dogs by vaccination, careful border control and preventing contact of domestic pets with wild animals. Pre-exposure immunization allows highly effective prevention and should be considered in individuals who are considered at high risk (e.g. vets, laboratory workers or those who handle imported animals) or those travelling to, living or working in endemic areas.

Table 8.21 Post-exposure treatment of rabies.

Examination of the biting animal
Ideally, the animal should be captured confined and observed for 10 days
If there is any clinical evidence of rabies, the animal should be killed and the brain examined for virus
Antigen detection in animals
Using fluorescent antibody techniques or cell culture (mouse inoculation)
Post-exposure prophylaxis
If there is any doubt about the possibility of rabies then post-exposure prophylaxis should be started immediately
Local wound care
Washed thoroughly with soap and water, debridement as necessary and tetanus prophylaxis
Active immunization
Using either human diploid cell vaccine or alternatively purified chick embryo cell culture vaccine in five doses given over 28 days. If infection occurs in a previously immunized individual only two booster doses are necessary
Passive immunization
Human rabies immunoglobulin should be given immediately before the vaccine. The wound should be infiltrated with the immunoglobulin and then a dose given intramuscularly

HTLV-1

HTLV-1 is a retrovirus that causes adult T-cell lymphoma/leukaemia and neurological involvement manifest as tropical spastic paraparesis and, less commonly, myositis and anterior horn cell involvement. HTLV-1 is a double-stranded RNA retrovirus with reverse transcriptase. Only a small proportion of people infected go on to develop neurological manifestations.

The virus is endemic in southern Japan, the Caribbean, South America and Africa. Risk factors for transmission of HTLV-1 include sexual contact, exchange of blood products and vertical transmission from mother to child (see also Chapter 15).

HTLV-1 associated myelopathy (TSP)

HTLV-1 associated myelopathy (tropical spastic paraparesis [TSP]) is a progressive inflammatory myelopathy evolving over many decades. The incubation period varies and may be years. Females are more commonly affected than males. Onset is variable but tends to be in the fourth or fifth decades; symptoms develop insidiously with a slowly progressive paraparesis predominantly affecting proximal musculature with brisk reflexes and extensor plantar responses. The lower limbs are overwhelmingly affected; bulbar muscles are not involved. Bladder dysfunction is manifest as urgency and incontinence; chronic retention and overflow may also occur leading to recurrent urinary tract infections; sexual dysfunction is common. There may be burning low back pain and painful dysaesthesiae in the legs. The myelopathy is occasionally associated with cerebellar ataxia. Examination shows mild to moderate progressive spastic pyramidal weakness which is more marked proximally. There is occasionally mild distal vibration sense absence to the ankles.

The major differential diagnosis is with primary progressive multiple sclerosis, hereditary spastic paraparesis (HSP) and primary lateral sclerosis. In TSP the brunt of pathological change is seen within the thoracic cord. The diagnosis is made on clinical grounds. HTLV-1 antibodies can be detected in serum and CSF using Western blot techniques. The CSF shows a mild lymphocytosis with elevated protein and local IgG synthesis. Oligoclonal bands are found that are specific for HTLV-1 core and envelope antigen. MRI shows peri-ventricular hyperintense lesions in many patients.

There is no effective treatment; transient benefit may be gained from steroids. The condition is relentlessly progressive, although the rate of evolution is variable.

Rarely, muscle inflammation is the only manifestation of HTLV-1 but it may accompany myelopathic or neuropathic features. Myalgia and progressive proximal muscle weakness develop over many months, occasionally associated with a dermatomyositis-like rash. The myositis is relentlessly progressive and does not respond to steroids. There have been no consistent reports of benefit from intravenous immunoglobulin (IVIG) or immunosuppression. Pathologically there is an inflammatory response with myofibre necrosis and regenerating fibres and mononuclear cell infiltrate.

HTLV I also causes both axonal and demyelinating neuropathies. Anterior and posterior uveitis have been described in association with HTLV-I. In these conditions the visual prognosis is good but there is a high relapse rate. A variety of other associations have been suggested, in particular between HTLV-I and cognitive impairment or other autoallergic conditions but these are unproven.

HTLV-II

HTLV-II is closely related to HTLV-I sharing 70% genomic homology. It is found in intravenous drug abusers and Native Americans but has not been clearly linked to any disease. HTLV-III was previously the term used for HIV-1 and HTLV-IV for HIV-2, but these terms have fallen out of usage. Recently, HTLV-III and HTLV-IV have been used to denote two newly characterized viruses of uncertain pathogenesis.

Progressive multifocal leucoencephalopathy

Progressive multifocal leucoencephalopathy (PML) is a rare condition in immunocompetent adults and is discussed in detail below in the context of HIV-related disease (see below).

Fungal infections

Fungi differ from bacteria by having a nucleus bounded by an organized membrane and a chitinous cell wall. They divide by mitosis, lack chlorophyll and are non-motile. Fungi exist in two forms: yeast and filamentous (hyphae and pseudohyphae). Yeasts are unicellular, multiply by budding and infections generally involve the CSF or meninges (Table 8.22). Filamentous fungi grow by extension of their hyphae, liberate spores and usually lead to parenchymous cerebral involvement. Fungal infections have increased because of the increased numbers of patients who are immunosuppressed due to HIV/AIDS, immunodeficiency or immunosuppression.

Fungi produce neurological disease by direct invasion, allergic phenomena and liberating toxins. Fungal meningitis generally develops insidiously over several days or weeks and is secondary to systemic mycosis elsewhere in the body. The CNS is seeded haematogenously either from a pulmonary or cardiac focus or secondary to direct spread from the sinuses or skull involving the subarachnoid space and leading to a basal meningitis. Fungal meningitis is characterized by meningism with subacute involvement of cranial nerves and an arteritis with thrombosis and cortical or subcortical infarction and micro-abscess formation.

Primary fungal pathogens include *Cryptococcus neoformans*, *Coccidioides immitis*, *Histoplasmosis*, *Blastomycoses* and *Paracoccidioides*. Secondary opportunistic pathogens are more common and occur with immune dysfunction, these include *Candida*, *Aspergillus* and *Mucormycosis*. *Cryptococcus*, *Aspergillus*, *Candida* and *Mucor* occur worldwide but *Histoplasmosis* and *Blastomyces* are generally confined to the Americas.

Risk factors

Fungal infection can occur as a consequence of direct inoculation of fungi followed penetrating trauma or neurosurgery. Cancer, chemotherapy and resulting neutropenia predispose particularly to *Candida* and *Aspergillus* meningitis and HIV to *Cryptococcus*, *Histoplasmosis* and *Coccidioides*. Other risk factors include:

- Pregnancy;
- Lymphoreticular malignancy including leukaemia and lymphoma;
- Diabetes;
- Organ transplantation;
- Severe burns;
- Connective and vascular disease; and
- Malignancy.

There is an extensive differential diagnosis of fungal meningitis summarized in Tables 8.16 and 8.17. The most import differential diagnoses are:

- Tuberculous meningitis;
- Granulomatous cerebral vasculitis (Churg–Strauss, Wegener's granulomatosis);

Table 8.22 Main fungal infections of the CNS.

Cryptococcus	Worldwide	HIV, cytotoxic drugs, HIV, RE malignancy	Granulomatous meningitis, hydrocephalus, raised intracranial pressure	Amphotericin B and flucytosine or fluconazole and itraconazole
Histoplasmosis	USA	HIV, steroids, organ transplant	Chronic basal meningitis or cerebritis Rarely, encephalitis or abscess	Amphotericin B, itraconazole or maintenance
Coccidiocoides	USA	HIV	Diffuse parenchymatous meningitis Meningoencephalitis Mass lesions	Amphotericin B followed by prolonged fluconazole maintenance
Candida	Worldwide	See text	Meningitis, vascular infiltration	Amphotericin B and flucytosine followed by fluconazole
Aspergillus	Worldwide	Neutropenia, immunosuppression	Cerebral abscess, diffuse granulomatous meningitis, vascular infiltration	Amphotericin B, debulking. Occ itraconazole
Mucormycosis	Worldwide	DM, malignancy		Ampohotericin B and surgical débridement

- Viral meningo-encephalitis;
- Sarcoidosis;
- Lymphoma;
- Carcinomatous meningitis;
- Partially treated bacterial meningitis;
- Other forms of chronic meningitis – lupus, sarcoid and idiopathic chronic meningitis.

The diagnosis of fungal meningitis is made on the basis of CSF examination which usually shows a mononuclear pleocytosis (20–500 cells/mm^3) with occasional predominance of polymorphonuclear cells especially in aspergillosis. The cell count may be reduced in immunosuppression. CSF staining and agglutinin testing is important in the diagnosis of *Cryptococcus* infection. In cultures *Candida* is identified in 2–3 days but dimorphic fungi such as *Histoplasma* may take several weeks to grow. Serology is occasionally helpful.

CT and MRI imaging may show meningeal enhancement and accompanying parenchymatous mass lesions, possibly with hydrocephalus. Meningeal biopsy is only occasionally of value.

True yeasts

Cryptococcus neoformans

Cryptococcus neoformans is an encapsulated yeast which is the most common pathogen causing fungal meningitis. It occurs in bird excreta and has a worldwide distribution. *Cryptococcus* characteristically occurs in patients with HIV, or who have received cytotoxic drugs or steroids and is also associated with sarcoid and reticulo-endothelial malignancy. Infection may remain dormant for many years or lead to immediate local pulmonary or disseminated infection.

Cryptococcus occurs as a result of inhalation of small yeast forms into the respiratory tract. There is an acute or subacute granulomatous meningo-encephalitis with meningism, headache and pyrexia, culminating in the progressive development of raised intracranial pressure due to hydrocephalus. There may be multiple cranial nerve palsies or focal neurological features including paraparesis, hemiparesis and ataxia. Visual impairment and cerebral infarction also occurs. The onset may be subacute over many weeks with cognitive impairment and dementia. The diagnosis is based on culture, direct observation with India ink staining, CSF fungal culture or crytococcal antigen testing which is both specific and sensitive. The CSF shows a variable lymphocytic pleocytosis.

The outcome of cryptococcal disease is variable. Untreated it tends to become disseminated and fatal within a few weeks but more often infection leads to persistently raised intracranial pressure with repeated lumbar puncture being necessary. It accounts for up to 20% of all AIDS-related deaths.

Cryptococcus is treated with an induction phase of intravenous amphotericin B and flucytosine. An alternative regimen is fluconazole or itraconazole for 8–10 weeks. Because of the high relapse rate in AIDS patients the third level of treatment using fluconazole 200 mg/day as a lifetime suppressive agent is recommended. Persistent raised intracranial pressure may need to be treated with recurrent lumbar punctures or ventriculoperitoneal (VP) shunt.

Histoplasmosis

Histoplasmosis usually manifests as a respiratory illness that resembles miliary TB. It is associated with AIDS, steroids and organ transplantation. In disseminated histoplasmosis, CNS involvement occurs in up to 20% of patients with a chronic basal meningitis or cerebritis. Less often there may be hydrocephalus, encephalitis, cerebral or spinal cord abscess. The diagnosis is made on the basis of CSF cultures positive in about 30%, microscopy is usually negative. CSF antigen detection is also possible but there is a high incidence of false positives. Treatment is with amphotericin B but relapses are common and maintenance with itraconazole is indicated. Similar chronic basal meningitis occurs with blastomycosis and actinomycosis.

Coccidiomycosis

Coccidiomycosis occurs particularly in the USA and is caused by air-borne spores. The onset is usually with a self-limiting flu-like illness and pulmonary infiltrates but the coccidioides may disseminate causing a chronic diffuse parenchymatous basal meningitis or meningo-encephalitis. Lytic skull and vertebral lesions occur and intracranial mass lesions may lead to communicating hydrocephalus. The diagnosis is made on the basis of culture and CSF positivity to complement fixation tests. Treatment is with intravenous amphotericin B given over a prolonged period of time followed by prolonged or lifelong treatment with fluconazole.

Pseudohyphae

Candida albicans

Candida albicans is a normal commensal but is the most common cause of fungal meningitis in neonates and young children.

Risk factors

- Neutropenia;
- Immunodeficiency (acquired in congenital shunt infection);
- Immunocompromised hosts;
- HIV;
- Organ transplants;
- Severe neutropenia;
- Diabetes;
- Severe burns;
- Use of total parenteral nutrition;
- Malignancy;
- Debility;
- Steroids and broad-spectrum antibiotics; and
- Postoperative neurosurgery.

Candidiasis may involve the lungs, heart, urogenital system and skin. There may be an acute meningitic illness with headache and fever but diffuse infiltration occasionally leads to a small vessel thrombosis with microinfarcts particularly in the middle cerebral artery territory. There may also be haemorrhage from rupture of mycotic aneurysms. Rarely, there is a subacute onset where invasion of the subarachnoid space occurs. Patients may have an indwelling VPshunt or ventriculostomy in place and are often receiving prophylactic antibiotics.

The diagnosis is made on the basis of clinical features together with the CNS showing a mild pleocytosis and a low glucose. CSF staining has a low yield (up to 20%) but in nearly half of these cases the diagnosis can be confirmed by culture. The CSF can be examined for other products of candidal metabolism. The mortality has been reduced from 10% to 20% with the use of amphotericin B and flucytosine because of its synergistic action. Treatment should be continued for 6–8 weeks and shunt replacement may be necessary. The prognosis for candidiasis remains variable with a mortality rate of up to 30% in patients with HIV but generally about 10%.

True hyphae

Aspergillus fumigatus

Aspergillus fumigatus accounts for about 5% of CNS fungal infections and carries a poor prognosis. It is associated with prolonged neutropenia, immunosuppression and parenteral drug abuse. Aspergillosis occurs as a complication of sinusitis, otitis or mastoiditis. Manifestations include cerebral abscess, diffuse and granulomatous meningitis but there is direct hyphal invasion of the cerebral blood vessels with thrombosis, necrosis and haemorrhage, particularly involving the posterior circulation. Intracranial mass lesions also occur which may be solitary or, less commonly, multiple. Progressive vascular infiltration may lead to multiple mycotic intracranial aneurysms clinically manifest as encephalopathy, seizures and focal neurological deficit. Haematogenous spread occurs. The diagnosis is difficult as cultures are insensitive but the products of metabolism may show evidence of aspergillus. Treatment is both medical and surgical involving debulking and specific treatment with amphotericin B (0.7–1.0 mg/kg/day) but higher doses may be used although the treatment is not as effective as in *Cryptococcus*. In some circumstances, the addition of itraconazole 200 mg 12 hourly helps. The prognosis is poor often because of the poor host status and the lack of response to therapy.

Mucormycosis

Mucormycosis is a rare fungal infection which is associated with malignancy, diabetes, steroids, pregnancy or drug addiction. There may be malignant infiltration of cerebral vessels with hyphae commencing in the nasal turbinates and paranasal sinuses and spreading along the infected vessels to the retro-orbital tissue. Cavernous sinus or internal carotid artery thrombosis and involvement of the adjacent brain contribute to haemorrhagic infarction. Ocular involvement is manifest as central retinal and ophthalmic artery occlusion or optic nerve compression. Treatment is with rapid correction of hyperglycaemia and acidosis, surgical debridement and amphotericin B but the prognosis is poor.

Parasitic disease of the nervous system

For the parasitic causes of CNS lesions see Tables 8.23–8.25.

Neurocysticercosis

Neurocysticercosis is caused by infection of the human brain by the larvae of the *Taenia solium*. It is the most common cause of acquired epilepsy in most low income countries and of major importance worldwide.

Cysticercosis occurs when humans become the intermediate host in the life cycle of the pork tapeworm (*Taenia solium*) by ingesting its eggs from contaminated water, food or by spread from food handlers who harbour the adult parasites in their intestines. Eating infected pork in which the larval cysts or adult tapeworm may be ingested leads to adult tapeworm infection (taeniasis) but transmission does not occur because the infected pork does not contain the eggs that cause cysticercosis. If the eggs are ingested they hatch into oncospheres in the intestine, these cross the intestinal wall and enter the bloodstream being carried to the tissues where the larvae (cysticercus) develop. Cysticerci are vesicles consisting of a wall and scolex. The main target organs of the cysticerci are the eye, skeletal muscle and the nervous system where cysticerci may develop in the brain parenchyma, subarachnoid space, ventricular system or spinal cord. Parenchymatous cysts develop in the cerebral cortex or the basal ganglia

Table 8.23 Parasitic causes of CNS lesions.

Nematodes (roundworms)
Trichinosis
Angiostrongylodiasis (*Angiostrongylus cantonensis*)
Strongylodiasis (*Strongyloides stercoralis*)
Visceral larva migrans (*Toxocara canis*)

Cestodes (tapeworms)
Cysticercosis (*Taenia solium*)
Hydated disease (Echinococcus)
Coenuriasis (*Multiceps*)
Sparganosis (*Spirometra*)

Trematodes (flukes)
Schistosomiasis (*Schistosoma japonicum, S. mansoni, S. haematobium*)
Paragonimiasis

Protozoa
American trypanosomiasis (Chagas disease)
African trypanosomiasis (sleeping sickness)

Table 8.24 Nematodes (roundworms).

Angiostrongyloides	Ingestion of raw or inadequately cooked shellfish or snails	Asymptomatic or associated with pruritus, abdominal pain. Neurological involvement is rare – may be chonic meningitis with headache, progressive cranial neuropathy, spinal cord involvement or retinal detachment CSF eosinophilic pleocytosis and raised protein. Larvae may be found in biopsy or the CSF Imaging shows meningeal enhancement with oedema and high signal in the basal ganglia Treatment is supportive
Strongyloides	Human intestinal infection Associated with poor sanitation Occurs on contact with the parasite in contaminated water or by direct penetration of the skin	Migrates via the venous circulation to the lungs and small intestine where it remains dormant for many years May subsequently reinfect the host and render them liable to secondary bacterial infection Affects the lungs and gastrointestinal tract but rarely may involve the CNS leading to encephalopathy, meningism and, rarely, vascular involvement including mycotic aneurysms, intracerebral haemorrhage or vasculitis Serum eosinophilia Larvae can be identified in stool, serum, CSF or peritoneal fluid Antibodies can be detected with immuno assay MRI shows atrophy and may show the presence of mycotic aneurysms or abscesses Treatment is with ivermectin (alternatives includes thiabendazole, albendazole or mebendazole)
Toxocara canis	Ingestion of parasites after contact with infected cats or dogs in whom the excreted eggs survive for many years	Endemic throughout the world The eggs hatch into larvae, which migrate to the liver and then to the viscera leading to an inflammatory response and granuloma formation Infection is usually mild and self-limiting but visceral larvae migrans may migrate to the lungs, liver, kidney, heart muscle, brain or eyes and ocular involvement can cause ocular neuritis and blindness. Cognitive impairment occasionally occurs with CNS involvement and there may be a dementia The diagnosis is difficult because the eggs are not excreted in the faeces Serum and CSF eosinophilia Antibody testing on CSF confirms the diagnosis Imaging may show subcortical and white matter disease suggesting a vasculitis Treatment is with diethylcarbamazine or alternatively mebendazole and albendazole

CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

Table 8.25 Cestodes (tapeworms).

Echinococcus (Hydatid disease)	The definitive host is canine Humans and sheep are infected by ingesting eggs excreted by infected animals and the source is usually water or vegetables contaminated by canine faeces After ingestion the parasite rapidly disseminates to the liver, lungs and vertebrae	Single hydatid cyst in the liver CNS involvement is also characterized by cyst formation causing compression of the brain or intracerebral blood vessels which may manifest as raised intracranial pressure with headache, nausea, vomiting and seizures and is generally difficult to distinguish from cysticercosis. The cysts may also cause compressive spinal cord lesions *Investigations* Elevated ESR, serum oesinophilia and positive immunophoresis testing Imaging confirms the presence of cysts (often multiple) of various sizes *Management* Surgical intervention is necessary to remove enlarged cysts with mass effect. Medical treatment is with albendazole
Sparganosis	Larval form of the tapeworm – contracted from contaminated water or eating undercooked fish	Invasion of the CNS occurs occasionally and there may be focal neurological features including seizures and hemiparesis *Investigations* Peripheral eosinophilia Parasite may be demonstrated in human tissue specimens. Immunofluorescent antibody techniques are sensitive and specific Imaging will show calcified lesions *Treatment* Praziquantel – only moderately successful and surgical excision of the parasite may be necessary

ESR, erythrocyte sedimentation rate.

because of the relatively high blood flow to these areas. Subarachnoid cysts may be larger and lodge within the cortical sulci or the CSF cisterns at the base of the brain. They may also involve the subdural space, the sellar region, the eye and the spinal cord. Cysticerci elicit a mild inflammatory response when they enter the nervous system and either remain viable for many years or enter into a process of degeneration that ends with their death. Following death, cysticerci undergo progressive involution in which the cyst is surrounded by a thick collagen capsule and adjacent brain parenchyma develops astrocytic gliosis and diffuse oedema. This progresses to granuloma formation and then calcification and astrocytic change when the oedema subsides. Cysticerci in the meninges induce an intense inflammatory response in the subarachnoid space with formation of a dense exudate leading to leptomeningeal thickening which may cause hydrocephalus or occlusion of the vessel lumen and cerebral infarction.

Clinical features

Infection is commonly asymptomatic. Epilepsy is the most common presentation – the seizures are usually generalized tonic–clonic or simple partial but can occasionally be complex partial. Focal signs may develop and hydrocephalus is commonly manifest as intracranial hypertension. Cognitive function may be impaired. Intrasellar cysticerci present with visual field loss and endocrine disturbances from pituitary involvement while ocular cysticerci cause decreased visual acuity or visual field loss. Spinal cord involvement is characterized by root pain or motor and sensory deficits that vary according to the level of the lesion. Massive infection of striated muscle may lead to generalized weakness associated with progressive muscle enlargement.

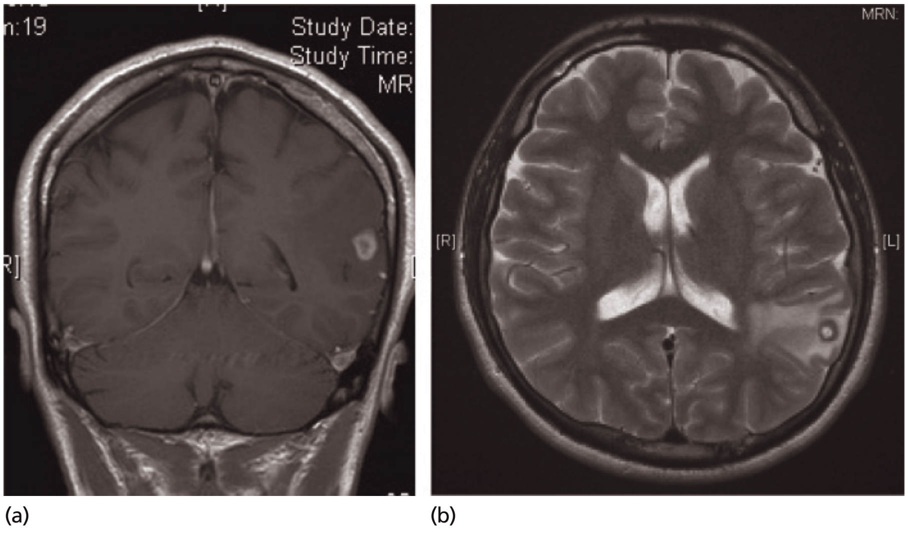
Neuroimaging

Plain films may show cigar-shaped soft tissue calcification or direct visualization of cysticerci in the anterior chamber of the eye or in muscles. In countries where neurocysticercosis is prevelant, small <1 cm brain lesions are often regarded as neurocysticercosis cysts unless proved otherwise. CT scan may show viable cysts which appear as hypodense rounded cystic lesions which may enhance after administration of contrast. The scolex can occasionally be seen as a hyper-intense dot in the interior of the cyst. Degenerating cysts appear as contrast enhancing rings on FLAIR MRI sequences (Figure 8.8). There may be hydrocephalus and abnormal enhancement of the leptomeninges is characteristic. Cysticerci should be distinguished from lesions of tuberculosis which tend to be larger and to have mass effect. The differential diagnosis also includes tuberculoma and tumours, particularly glioma.

Stool examination may reveal the ova of *Taenia solium*. Serological investigations including enzyme-linked immunoelectrotransfer blot with purified glycoprotein antigens (Western blot) can be undertaken on serum or CSF. Cysticerci outside the nervous system may be noted subcutaneously on X-ray or by muscle biopsy.

Management

There remains uncertainty about the value of medication in the treatment of neurocysticercosis because many of the clinical manifestations are brought about by the effects of established deficit caused by calcified cysts rather than active lesions. In most patients a single enhancing lesion may disappear spontaneously. However, current evidence favours treatment in patients with viable intraparenchymal or extraparenchymal parasites. This is both symptomatic and anti-parasitic treatment. Albendazole (<15 mg/kg/day for 1 month) has a greater effect on killing parasites but praziquantel has also been widely used. There is considerable variability in the dose and duration of treatment. A single course of albendazole or praziquantel will kill 60–85% of viable brain cysts leading to a faster radiological resolution of the cysts. Corticosteroids are indicated in the presence of encephalitis



(a) (b)

Figure 8.8 Isolated lesion of neurocysticercosis shown on: (a) MRI T1W; and (b) MRI T2W.

Table 8.26 Trematodes.

Paragonimus	Only mammalian lung fluke that can infect humans	CNS involvement is extremely rare Chronic meningoencephalitis. Focal lesions including transverse myelitis, myelopathy and seizures *Investigations* Serum and CSF eosinophilia often marked Demonstration of eggs in CSF or on brain biopsy material Serum antibody tests positive. Imaging showing multiple clusters of calcified density in the right frontal and temporal region *Treatment* Praziquantel (Steroids synergistic with large lesions)

CSF, cerebrospinal fluid.

angiitis or chronic meningitis that causes progressive entrapment of the cranial nerves. Antiepileptic medication may need to be life-long. Ventricular shunting to resolve hydrocephalus may be necessary but this is associated with a high level of shunt malfunction.

Trematodes

See Table 8.26 for trematodes.

Schistosomiasis (bilharzia)

Schistosomiasis occurs in up to 300 million people worldwide. There are five forms but CNS involvement occurs particularly with *Schistosoma mansoni*, *S. haematobium* and *S. japonicum*. Infection is acquired from water where there is poor sanitation or water supply. The larva invades the skin and migrates into the venous system. Subsequent spread depends on the species involved. The eggs of *S. japonicum* cause 60% of all schistosomal brain infections while *S. mansoni* tends to be confined to the spinal cord and *S. haematobium* can involve brain or cord. Eggs enter the CNS and cause a granulomatous response which walls off the invading parasite. The granulomas expand, become exudative and necrotic, involving vascular walls as well as local tissue.

The onset is with an acute pyrexia with urticarial swelling, myalgia, eosinophilia and bloody diarrhoea. Neurological involvement occurs in <5% of patients and develops after weeks or months when the eggs migrate through the vascular system to the brain or spinal cord. Mass lesions may be produced by expanding granulomas leading to raised intracranial pressure or erosion of vessel walls culminating in intracranial haemorrhage. Spinal cord involvement may be caused by granuloma formation and transverse myelitis can occur although cauda equina and conus syndromes are also characteristic.

Diagnosis is made by detection of the eggs in stool, urine or tissue biopsy. Antibody detection, using ELISA, is possible but this is not reliable. CT scan shows single or multiple hyperdense lesions caused by granuloma formation, which is inflammatory and surrounded by oedema with variable contrast enhancement.

Treatment

Treatment is conventionally with praziquantel, which is effective against all schistosome species and curative for <90% of patients. If patients continue to excrete the eggs then it is necessary to have a further course of treatment. Alternative treatments include niridazole or artemether, which kills immature migrating larvae and is synergistic with praziquantel. Steroids are used for lesions if there is extensive surrounding oedema and large granulomas may need to be excised surgically.

Protozoa

American trypanosomiasis (Chagas disease)

American trypanosomiasis (Chagas disease) is caused by *Trypanosoma cruzi*, which is endemic in South and Central America. Infection occurs secondary to contact with raduviid bug, ingesting guinea pig excretia, blood transfusion or organ transplantation. Larval eggs are taken through the site of pruritic skin lesions. The larvae then mature and are transported by the bloodstream to distant sites. They divide intracellularly before rupture of the cell releases the infectious parasite and inflammatory substances.

Chagas disease has an onset with malaise, myalgia, headache and anorexia. There is unilateral or bilateral periorbital oedema (Romana's sign). Cardiac failure and intestinal involvements are common. Meningo-encephalitis may occur in a minority of patients depending on the severity of infection and extent of host immune response. The diagnosis is made by CSF demonstration of trypanosomes. Serum antibody detection tests are sensitive and specific for acute and chronic forms. MRI scanning may show one or more ring enhancing lesions involving the grey and white matter. Acute Chagas disease can be eradicated by benzonidazole or nifurtimox but chronic infection remains symptomatic and is difficult to clear.

African trypanosomiasis (sleeping sickness)

African trypanosomiasis (sleeping sickness) occurs in humans in two forms: *Trypanosoma brucei gambiense* (West African) and *Trypanosoma brucei rhodensiense* (East African). The condition is widespread throughout sub-Saharan Africa. The vector of both species is the tsetse fly which feeds from infected animals. A superficial chancre forms at the site of the bite and the parasite larvae migrate, via the bloodstream, to the lymphatic vessels before maturing and reproducing. There is then a secondary spread of mature forms to the lymph nodes, spleen, liver, heart, endocrine system, eye and CNS leading to a host immune response and meningo-encephalitis.

West African trypanosomiasis is slow or indolent in onset and characterized by rash, intermittent fever and lymphadenopathy. Involvement is episodic. The East African form is more aggressive with behavioural disturbance, psychiatric manifestations including anxiety agitation and manic and uncontrolled behaviours. Sleep disruption occurs with day–night reversal and uncontrolled urges to sleep. The condition progresses to motor disturbances including ataxia, rigidity, akinesis and progressive pyramidal signs but meningism is rare. Visual involvement includes optic neuritis, optic atrophy and papilloedema. Death occurs as a result of coma, secondary infection or cardiac involvement. The diagnosis of trypanosomiasis can be made by direct observation in wet preparations of stained blood, CSF or biopsy. However, antibody and PCR tests are unreliable. MRI may show focal high signal abnormalities.

The treatment is suramin and pentamidine but this is not suitable if there is CNS involvement when melarsoprol or eflornithine are recommended.

Toxoplasma gondii

Toxoplasma gondii is an intracellular protozoan which is widely distributed. Invasion occurs as a result of ingestion of uncooked meat. *Toxoplasma* may invade multiple organs but in immunocompetent individuals infection is generally asymptomatic or associated with a mild mononucleosis-like illness with lymphadenopathy and a non-specific systemic illness. However, severe disease may occur in the immunocompromised patient and this is discussed below.

Malaria

Malaria is the most important parasitic disease of humans and it is estimated that >5% of the world population has been infected. Each year >500 million cases of malaria occur worldwide, 90% of these are in Africa or South-East Asia and the condition accounts for 200 million deaths per year.

Malaria is caused by four parasitic protozoa of the genus *Plasmodium*: *P. vivax*, *P. falciparum*, *P. ovale* and *P. malariae*. It is only *P. falciparum* that can cause severe generalized disease and in particular cerebral malaria. The protozoa is transmitted by the female *Anopheles* mosquito which feeds at night-time although, rarely, transmission may also be transplacental or from contaminated needles. Infection is initiated by sporozoites injected in the bite of the mosquito. The protozoa undergoes a complex life cycle in the human host in which the sporozoites mutiply within hepatocytes, producing thousands of multinucleated merozoites which enter the red blood cells and become mature forms (trophozoites and schizonts) before rupturing and releasing further merozoites. In falciparum malaria the red blood cells become distorted and excessively adherent binding to endothelial cells and causing sequestration, clumping and eventually vascular obstruction within the cerebral vessels. There is also an associated suppression of haemopoiesis leading to anaemia, thrombocytopenia and hepatosplenomegaly.

Plasmodium vivax, *P. ovale* and *P. malariae* are either asymptomatic or cause recurrent episodic fever of varying severity. In *P. falciparum* malaria, clinical manifestations depend on the load of parasite and the immune state of the host. Onset is with a flu-like illness, headache, fever and muscle aches. There are often paroxysms of rigor and shivering in between the pyrexia with extensive diaphoresis and hypothermia. Cerebral malaria is manifest by the onset of coma often heralded by focal or generalized seizures. Raised intracranial pressure develops rapidly, leading to possible brainstem herniation; in addition, vascular engorgement leads to the development of cerebral arterial occlusion, aneurysms or intracranial haemorrhage. A subacute syndrome or diffuse symmetrical encephalopathy may also occur associated with brainstem signs, eye movement abnormalities, pyramidal signs or extrapyramidal movements including choreoathetosis and myoclonus. Retinal haemorrhages are characteristic. Severe malaria is also associated with generalized systemic involvement including renal and hepatic failure, hypoglycaemia, bleeding diathesis, circulatory collapse and pulmonary oedema.

Diagnosis

The diagnosis of cerebral malaria is made on thick blood films and a light microscopy ensuring that large amounts of blood are available and a minimum of 100 fields are observed. Thin film assessment allows species recognition. Newer antigen tests are now available based on recognition of the HRP-2 antigen of falciparum. PCR techniques are specific and sensitive to plasmodium, but do not give an estimate of the parasite load.

Coma occurring in patients with cerebral malaria carries a fatality rate of up to 20% when appropriately treated and is invariably fatal if untreated. Complications include cerebral or dural venous thrombosis and cortical infarction. The management of acute malaria depends on the infecting species, the severity of parasitaemia, the pattern of clinical involvement and potential drug resistence.

Acute management

Acute management of cerebral malaria involves supportive care with appropriate attention to ventilation, fluid balance, renal

Table 8.27 Antimicrobial treatment for malaria.

Plasmodium *P. malariae* *P. ovale* *P. vivax* Chloroquine sensitive *P. falciparum*	Chloroquine and primaquine
Chloroquine resistant *P. falciparum*	Quinine sulphate and tetracycline (alternative to tetracycline is sulfadoxine and pyrimethamine or amiodaquine or doxycycline)
Multi-drug resistant *P. falciparum*	Mefloquone or artesunate or sulfadoxine and pyrimethamine or proguanil and atovaquone
Severe complex multi-drug resistant *P. falciparum* (particularly if mefloquine resistant)	Quinine dihydrochloide

function and seizures. *P. falciparum malariae*, *P. ovale* and *P. vivax* should be treated with a standard course of chloroquine over 48 hours. In severe cases it may be necessary to treat with an intravenous infusion of chloroquine. Primaquine may be added to eradicate the exerythrocytic forms and prevent relapses (Table 8.27).

Because chloroquine-resistant *P. falciparum* is widespread, treatment of mild infections is with oral quinine sulphate followed by doxycycline or clindamycin to eradicate remaining asexual forms. Alternatives include mefloquine or co-artemether. Severe *P. falciparum* should be treated in intensive care with intravenous quinine sulphate and meticulous attention to fluid balance, renal and cardiac function. Alternative treatments for *P. falciparum* or cerebral malaria include quinidine, artemether or artesunate.

Prevention

Although the complete genome of the *Anopheles* mosquito and *P. falciparum* has been sequenced, this has not yet led to new therapy and therefore traditional prophylaxis is still mandatory. Recommendations concerning appropriate prophylaxis vary depending on the characteristics of malaria and drug resistance in particular areas.

Whipple's disease

Whipple's disease is a multi-system disorder that usually presents with systemic and gastrointestinal features before neurological involvement develops. However, the condition may occasionally present with neurological features or these may be the only manifestation. Patients usually develop weight loss in association with gastrointestinal disturbance including abdominal pain, diarrhoea and steatorrhoea. Joint pain occurs as a consequence of a seronegative migratory arthropathy. There may be a low grade chronic pyrexia and the development of lymphadenopathy, splenomegaly and hyperpigmentation. Cardiac involvement may include endocarditis, constrictive pericarditis and culture negative endocarditis.

CNS involvement occurs in up to 40% of patients, often late in the course of the disease. The most common manifestation is slow onset of cognitive change including memory loss, behaviour and personality change which may evolve into frank dementia. Ocular involvement is also frequently seen with inflammatory changes causing retinitis or uveitis but there may also be papilloedema and progressive optic atrophy. Supranuclear vertical gaze palsy may occur in association with the characteristic movement disorders of oculo-masticatory myorhythmia in which there is an associated repetitive movement of the masticatory muscles that persists during sleep or oculofacial skeletal myorhythmia that involves the facial and other musculature. Seizures and myoclonus occur in up to one-quarter of patients in whom there is neurological involvement and there may also be a progressive ataxia. Rarely, the level of consciousness may be affected with progressive obtundation and even coma. Thalamic involvement causing polydipsia, hyperphagia, insomnia or hypersomnia is described.

The condition is caused by a Gram-positive bacillus *Tropheryma whippelii.* This is a slow-growing organism which is ubiquitous. It is identified in biopsy of the jejunal mucosa which shows macrophages filled with Periodic acid – Schiff (PAS) positive intracellular inclusions which contain the organism. Similar staining may be seen in biopsies of lymph nodes, heart valves and cerebral tissue and in the CSF. Diagnostic PCR assay for *T. whippelii* are increasingly used to establish and confirm the diagnosis of Whipple's disease. CSF is characterized by pleocytosis with an elevated protein. MRI may show diffuse high signal on T2 weighted images particularly affecting the frontal cortex, basal ganglia and peri-ventricular white matter but the hypothalamus and cortex may also be involved. Occasionally, mass lesions may develop with ring enhancement. There may also be diffuse atrophy or focal abnormalities and, occasionally, hydrocephalus.

Management remains unsatisfactory. Conventionally, patients have been treated with parenteral penicillin and streptomycin followed by long-term tetracycline. Relapses occur and the outlook for recovery with neurological involvement is particularly poor. Newer recommendations suggest more intense and vigorous treatment is indicated in the presence of neurological involvement because of the likelihood of clinical relapses. Treatment should be with penicillin G and streptomycin in an induction phase with ceftriaxone maintenance followed by 6-month cyclical therapy with co-trimoxazole, doxycycline and cefixime. Although antibiotics are usually given for 1 year it has been increasingly argued that with neurological involvement treatment should be given indefinitely because of the high likelihood of relapse when therapy is stopped.

Neurological disorders resulting from HIV

It is now more than 25 years since the onset of the HIV/AIDS pandemic. Although it was soon apparent that the CNS was frequently involved with opportunistic infections, it was subsequently recognized that patients developed complications from the HIV genome itself such as dementia, myelopathy and neuropathy. With the introduction of highly active antiretroviral therapies (HAART) since 1997 the incidence of opportunistic infections and tumours, as well as the HIV-related complications, have drastically reduced. This group of patients now present with problems resulting from drug side effects such as neuropathy, a metabolic syndrome that may predispose to cerebrovascular disease and complications arising as a complication of immune reconstitution. In addition, because of the greater longevity, patients with HIV are now prone to the same disorders associated with ageing found in the non-infected population.

HIV is neuroinvasive (with invasion occurring early in the course of the infection), neurovirulent (causing a neuropathy, myopathy, myelopathy and encephalopathy) but not particularly neurotrophic. The virus is rarely isolated from the neurones of the peripheral or central nervous systems and productive infection is usually found within the associated inflammatory infiltrate, predominantly in macrophages and microglia.

Basic principles

As a result of immunosuppression, the clinical presentations may be atypical. For example, only one-third of patients with cryptococcal meningitis develop classic features of meningism. A low threshold for investigation with CT/MRI and lumbar puncture is necessary.

Because all areas of the neuro-axis in an HIV infected individual may be affected by different aetiological agents, the principle of 'Occam's razor' may not be applicable. For example, a patient may have a mass lesion in the brain resulting from toxoplasmosis, a concurrent HIV-related myelopathy and a drug-induced neuropathy.

Dual infections are relatively common and this possibility must be borne in mind when assessing a treatment response. For example, patients may have meningitis resulting from *Cryptococcus neoformans* and *Mycobacteria tuberculosis*.

At seroconversion, a glandular fever-like illness occurs in 70% of cases. In 10%, this may be associated with neurological symptoms and signs – aseptic meningo-encephalitis, acute disseminated encephalomyelitis (ADEM), transverse myelitis, polymyositis, brachial neuritis or a cauda equina syndrome. Guillain–Barré syndrome has also been described at seroconversion and during the asymptomatic phase of HIV infection although the CSF shows a significant pleocytosis in contrast to the findings in HIV-negative patients where CSF examination is usually acellular with a high protein.

During the asymptomatic phase of HIV infection, when there is no evidence of immunosuppression clinically and the CD4 count is above at least 350 cells/mm^3, there is no evidence of neurological symptoms or signs. This has been ascertained by a number of large cohort serial studies using clinical, neurophysiological, neuroradiological and neuropsychological methods of assessment. However, prior to the introduction of HAART, in up to 5% of cases HIV dementia was the AIDS defining diagnosis. HIV infection should therefore be considered in the differential diagnosis in any young patient presenting with cognitive impairment.

HIV infection may be associated with a vasculitis or a thrombophilic state with anticardiolipin antibody and lupus anticoagulant and therefore enters the differential diagnosis of young stroke.

CSF examination may be abnormal because of HIV infection per se even in the asymptomatic immunocompetent stages. These include a mild lymphocytic pleocytosis, an elevated CSF protein and oligoclonal bands. Conversely, as a result of HIV-induced immunosuppression, patients with meningitis or encephalitis may have normal CSF indices. The diagnosis of neurological disorders therefore relies on specific tests on the CSF such as the detection of cryptococcal antigen (by latex agglutination – CRAG), culture or using PCR techniques.

Serological studies, e.g. in toxoplasmosis, are unhelpful in making a diagnosis as used in immunocompetent cases as there is no diagnostic fourfold rise in IgM and IgG titres.

In patients who have not received HAART, the CD4 count is a useful guide in attempting to determine the specific aetiologies of opportunistic infections and tumours. For example, toxoplasmosis and cryptococcal meningitis occur with CD4 counts below 200 cells/mm^3; CMV retinitis, encephalitis and polyradiculopathy occur below 50 cells/mm^3. Complications resulting from *Mycobacteria tuberculosis* may occur at earlier stages when the CD4 count may be 350 cells/mm^3. In HAART exposed patients, these guidelines are less robust because even if there is a rise in the CD4 count, these lymphocytes may not be fully competent as some antigen-specific clones will have been lost.

Opportunistic infections and tumours in HIV

Toxoplasma gondii

Toxoplasma gondii is an obligate intracellular protozoan, whose definitive hosts include members of the cat family with humans acting as intermediate hosts. Human infection occurs by ingestion of oocytes in cat faeces and the ingestion of tissue cysts in undercooked meat. Variations in dietary habits explain the differing seroprevalence rates worldwide – 90% in French adults compared to 50% in the UK. Symptomatic toxoplasmosis is usually caused by reactivation of latent infection in immunosuppressed individuals. The risk of an HIV-infected patient who is seropositive for IgG *T. gondii* antibody developing toxoplasmosis is around 25%.

Toxoplasmosis is the most common cause of mass lesions in the CNS of HIV patients even in developing countries where tuberculosis is rife. Reactivation occurs when the CD4 count drops below 100–200 cells/mm^3. The clinical presentation is with headache, confusion and/or seizures in association with hemiplegia, dysphasia and visual field defects. Other clinical features include: a variety of movement disorders (choreoathetosis, dystonia and hemiparkinsonism); psychiatric illness such as depression and personality change resulting from frontal lobe pathology; brainstem syndromes and a rapidly progressive diffuse encephalitis. Rarely, the spinal cord may be involved with a myelitis or a cauda equina syndrome.

A definitive diagnosis of *Toxoplasma* encephalitis can only be made by brain biopsy. With increasing experience and pragmatism, it is now standard practice to treat any HIV-infected individual with a low CD4 count and mass lesions on imaging with anti-*Toxoplasma* therapy. A response, clinically and radiologically, confirms the diagnosis. Although negative blood serology makes the diagnosis less likely, this may still occur in up to 17% of cases. These latter cases are a result of impaired antibody synthesis with increasing immunosuppression and the occasional primary infection. It is useful therefore to document *Toxoplasma* serology at the time of HIV diagnosis. On imaging studies, preferably MRI, *Toxoplasma* lesions have a predeliction for the grey–white interface and the basal ganglia. There is normally mass effect with surrounding oedema with patchy enhancement. A single lesion or peri-ventricular lesions are more likely to be caused by primary CNS lymphoma, the main differential diagnosis that occurs with a similar clinical presentation and at similar low CD4 counts.

Response to treatment is seen in 90% of patients by the second week of treatment. It is prudent to re-image even if there is clinical improvement because it is not rare for some lesions to improve and others, such as those due to *M. tuberculosis*, to enlarge making it necessary to consider biopsy. The radiological improvement generally lags behind the clinical improvement. Patients who are HIV infected and who are seropositive for IgG against *T. gondii* should be offered primary prophylaxis with 980 mg co-trimoxazole (trimethoprim and sulfamethoxazole) when the CD4 count drops below 200 cells/mm^3. This also offers protection against *Pneumocystis jirovecii*.

Primary CNS lymphoma

Primary CNS lymphoma (PCNSL) is the second most common cause of mass lesions in adults and the most common in children with AIDS. Histologically, this is a high grade, non-Hodgkin B-cell lymphoma (Chapter 20). The Epstein–Barr virus is causally linked to PCNSL, with the identification of the viral DNA incorporated into that of the neoplastic cells.

The common presenting symptoms are headache with focal neurological deficits, altered level of consciousness and seizures. Brain imaging reveals enhancing mass lesions with surrounding oedema. These are similar to those found in toxoplasmosis. PCNSL is more likely to present with a single lesion than toxoplasmosis and is also more likely to invade the ventricular walls. Studies using thallium-201 single photon emission computed tomography (SPECT) suggest that it may be possible to differentiate between an abscess and a tumour with the former having little uptake compared with high uptake of the mitotically active lymphoma. CSF analysis is usually not performed because of raised intracranial pressure but when possible the identification of EBV by PCR is useful diagnostically with a sensitivity of 50–100% and a specificity of 94%.

There is no effective therapy for PCNSL and most patients succumb within 2–3 months. Radiotherapy may increase survival times by a few months. However, recent data suggest that treatment with HAART can also improve survival times.

Progressive multifocal leucoencephalopathy

Progressive multifocal leucoencephalopathy (PML) is caused by the reactivation of the JC virus (JCV; the initials of the patient from whom the virus was first isolated), a common polyoma virus, which infects 75% of the general population. As the virus is frequently excreted in the urine of healthy individuals, primary infection is postulated to occur via the urine–oral route.

Because impaired cell-mediated immunity is the major predisposing factor for the development of PML, prior to the AIDS epidemic, the condition was occasionally encountered in patients with lympho-proliferative disorders, sarcoidosis and those treated with immunosuppressive drugs, e.g. after transplant operations and systemic lupus erythematosus (SLE). HIV-induced immunosuppression currently accounts for 85% of cases of PML. Prior to HAART, 5% of AIDS patients developed PML with CD4 counts usually below 100/mm^3. However, after the introduction of HAART, PML has remained more prevalent than expected and this may be related to increased activation of JCV by the HIV proteins. The underlying pathology results from replication of the virus within the oligodendrocytes causing lysis and demyelination. It is unclear whether PML results from reactivation of the virus in the CNS following immunosuppression or if it is a result of invasion of the CNS by infected lymphocytes from the peripheral circulation.

The clinical presentation is with a progressive subacute focal deficit which may be hemiparesis, hemianopia or ataxia. Cognitive dysfunction is usually associated with focal neurological signs. Lesions adjacent to the cortex may occasionally result in dysphasia and seizures. Spinal cord involvement has not been described. In contrast to other more common causes of focal lesions found in HIV infected patients such as toxoplasmosis, there are usually no symptoms or signs of systemic infection or raised intracranial pressure. A cerebellar syndrome with only cerebellar atrophy on MRI scans may occur, pathological studies show JCV infection of the granular cells (JCV granule cell neuronopathy).

Cranial CT shows hypodense lesions. MRI shows large single or multiple lesions involving white matter, with scalloping at the grey–white interface; the parieto-occipital and frontal lobes are most commonly affected. The affected areas are low signal on T1 weighted images and hyperintense on T2 weighted sequences. This may help distinguish PML from HIV dementia. There is no mass effect but contrast enhancement may be seen and has been identified as a good prognostic marker.

Early in the AIDS epidemic the diagnosis was only possible by brain biopsy with the histological demonstration of demyelination, enlarged oligodendrocyte nuclei with JCV inclusion particles and bizzare enlarged astrocytes. Prior to the HAART era, JCV DNA could be isolated from the CSF by PCR with a sensitivity of 75% and a specificity of 99%. Since HAART, the sensitivity seems to have dropped to 58% perhaps because of decreased viral replication. The yield can be increased to 85% with repeated CSF examination in PCR negative cases but stereotactic brain biopsy may be necessary.

The treatment of PML in patients with HIV is two-pronged: improving the underlying immunosuppression with HAART and anti-JCV therapy. Institution of the former has resulted in fourfold improvement in survival, with some patients' neurological status stabilizing or improving. A number of drugs such as cytosine arabinoside (araC) given intravenously or intrathecally have anti-JCV activity but have not been shown to be of benefit. Alpha interferon has been used because of its antiviral and immune-enhancing effect in a pre-HAART retrospective open-labelled observational study. About one-third of patients showed some neurological benefit, with some also showing radiological improvement. The anti-CMV drug cidofovir, when used in conjunction with HAART, also increases neurological improvement or stability when compared to HAART alone and led to faster clearance of the virus from the CSF but this finding has not been consistent. Furthermore, cidofovir has a number of serious side effects – nephrotoxicity resulting from a dose-dependent renal tubular acidosis, neutropenia and ocular hypotonia.

Cryptococcal meningitis

In patients infected with HIV, meningitis caused by the fungus *Cryptococcus neoformans* occurs in 10% of patients with advanced HIV disease, usually when the CD4 count falls below 100 cells/mm^3. The incidence has fallen significantly since the introduction of HAART. *C. neoformans* is ubiquitous in the environment and is commonly found in the soil and in the excreta of pigeons. Pulmonary infection, usually asymptomatic, occurs by inhalation followed by haematogenous spread to the meninges.

The clinical presentation is usually with headache which initially maybe mild, fever and drowsiness. Only 30% of individuals present with features of meningism – photophobia, neck stiffness and a positive Kernig's sign. In 20% of cases there may be extra-neurological involvement with diffuse pulmonary infiltrates, lobar consolidation or cavitating lesions on chest X-ray, skin lesions (small papules which resemble molluscum contagiosum) and infection of the urinary tract.

Brain imaging may be normal or may reveal hydrocephalus, cryptococcomas, dilated Virchow–Robin spaces which are filled with the fungal organisms, and basal meningeal enhancement. Measurement of the serum cryptococcal antigen is a useful screening test in those with mild symptoms and, if positive, necessitates imaging and CSF examination. At lumbar puncture, CSF pressure is frequently elevated. In most cases there is a moderate mononuclear pleocytosis, an elevated protein and a low glucose; however, in 25%, the CSF maybe normal. The diagnosis is established by the identification of India ink positive hypae in 75% and the detection of cryptococcal antigen in 95% of cases. A number of poor prognostic markers have been identified:

- CSF opening pressure >25 cm CSF;
- Altered mental status;
- CSF cryptococcal antigen titre >1 : 1024;
- CSF white cell count <20 cells/mm^3; and
- Hyponatraemia.

Amphotericin B with or without flucytosine is the treatment of choice, but in patients with mild disease without any of the poor prognostic markers fluconazole maybe considered. Acute treatment should be continued until the CSF culture is sterile which may take 4–6 weeks, following this, secondary prophylaxis should continue with fluconazole. HAART should be commenced on complete recovery if the patient was not already receiving this. However, if HAART is started too soon there is a risk of developing the immune reconstituition inflammatory syndrome (IRIS).

Raised intracranial pressure, unrelated to hydrocephalus, should be managed aggressively, as it may result in visual loss, by repeated lumbar puncture with high volume CSF removal and, if required, by the placement of a lumbar or ventricular drain. Acetazolamide may also be used as an adjunct.

Cytomegalovirus infection

CMV infections of the nervous system occur when the CD4 counts are very low – usually below 50 cells/mm^3 and usually associated with CMV disease elsewhere in the body. Prior to HAART, CMV retinitis was the most common cause of blindness in this group of patients. Typically, patients present with painless visual loss. Fundoscopy shows extensive haemorrage and necrosis with the so-called ketchup and cheese appearance. CMV encephalitis presents with a rapidly evolving encephalopathy with focal deficits often involving the brainstem. Imaging studies have shown a range of abnormalities including a peri-ventriculitis, non-enhancing hypodense lesions resembling PML and, rarely, single or multiple enhancing mass lesions. CMV lumbosacral polyradulopathy presents subacutely with back pain and progressive weakness of the legs with sphincter involvement. Imaging studies may be normal or show thickened nerve roots. CSF examination, which is essential to exclude other causes of a polyradiculopathy such as syphilis and lymphomatous infiltration, shows a polymorphonuclear pleocytosis which is unusual in a viral infection, an elevated protein and low glucose. CMV DNA can be isolated from the CSF by PCR. CMV has also been associated with a mononeuritis multiplex, usually in the context of CMV elsewhere such as a retinitis. The diagnosis is confirmed by sural or superficial peroneal nerve biopsy.

Herpes varicella zoster

Although dermatomal zoster (shingles) is common in the HIV population, occasionally patients may progress to a severe myeloradiculopathy. After dermatomal zoster, especially involving the trigeminal nerves, VZV involvement of the small cerebral vessels can present with a granulomatous angiitis. The clinical presentation is with headache, progressive focal neurological deficits and seizures. MRI shows multiple T2 abnormalities on T2 weighted images. The CSF is diagnostic with the identification of viral DNA by PCR. Treatment is with high-dose aciclovir and corticosteroids.

Herpes simplex

Herpes simplex type 2 has been rarely associated with a rapidly progressive myelitis in those presenting with back pain, progressive leg weakness and sphincter disturbance. MRI shows an oedematous cord. The diagnosis is confirmed by the identification of viral DNA in the CSF.

Neurological complications directly resulting from HIV

HIV enters the nervous system early in the course of infection. The evidence for this includes the neurological seroconversion illness, the presence of CSF abnormalities in asymptomatic immunocompetent individuals and the presence of HIV DNA in brain pathological studies of asymptomatic HIV-infected patients who died from other causes. In one case of iatrogenic HIV transmission caused by a blood product given intravenously, the patient died 15 days after the accident from an unrelated cause. HIV DNA was identified in the brain (Table 8.28).

The mechanism of viral entry into the CNS remains controversial because the blood–brain barrier is an effective physical and metabolic barrier. The most accepted current theory is the Trojan horse mechanism, which proposes that HIV viral entry through the blood–brain barrier occurs via infected macrophages from the peripheral circulation. The choroid plexus, which resides outside the blood–brain barrier, is another potential site of viral entry because the choroid capillary endothelial cells are freely permeable with the stromal cells containing monocytes and macrophages.

Within the brain, infection is localized primarily within the microglial cells and macrophages which are derived from peripheral blood monocytes. HIV does not infect neuronal cells even though neuronal cell death is an important aspect of the neuropathology of HIV dementia. There is some evidence suggesting there is a low level of astrocyte infection; this may be important because the astrocytic foot processes are an integral part of the blood–brain barrier and a low level of infection may be enough to disrupt functioning of the tight junctions between the endothelial cells. Although demyelination is also a feature of HIV brain disease, infection of the oligodendrocytes has rarely been reported.

The neurovirulence of HIV occurs later in the course of the disease when immunosuppression develops and HIV acts like an opportunistic infection. It remains uncertain if this is a result of activation of the virus seeded in the nervous system early in the course of disease or trafficking of new HIV viral species from the peripheral circulation, or both. There is no doubt that since the introduction of HAART, the incidence of HIV dementia has reduced suggesting that suppression of HIV in the peripheral circulation has a crucial role (Table 8.29).

Table 8.28 Neurological complications in HIV-1 infection.

Caused by HIV
Peripheral neuropathy
Distal sensory peripheral neuropathy
Inflammatory demyelinating neuropathy (GBS and CIDP)
Vasculitic neuropathy
Diffuse inflammatory lymphocytosis syndrome
HIV associated dementia
Vacuolar myelopathy
HIV polymyositis
Opportunistic infections
Toxoplasmosis gondii – abscesses, encephalitis
Cryptococcal neoformans – meningitis
Mycobacterium tuberculosis – meningitis, abscesses, tuberculoma, myeloradiculopathy
Cytomegalovirus – encephalitis, retinitis, lumbosacral polyradiculopathy, vasculitic neuropathy
JC virus – progressive multifocal leuco-encephalopathy
Herpes varicella zoster – encephalitis, CNS vasculitis, myelitis
Herpes simplex – encephalitis, myelitis
Tumours
Primary CNS lymphoma (EBV-related)
Metastatic systemic lymphoma
Cerebrovascular disease
HIV-associated thrombophilia
Cardioembolic – endocarditis, infectious and marantic
Vasculitis – HIV-associated, infectious (varicella zoster)
Drug-related complications
Peripheral neuropathy
ARV drugs (ddC, ddI, d4T)
Other drugs (thalidomide, isoniazid, dapsone)
Myopathy (AZT)

ARV, antiretroviral; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; EBV, Epstein–Barr virus; GBS, Guillain–Barré syndrome.

HIV-associated dementia (HIV encephalopathy, HIV associated cognitive motor complex, AIDS dementia complex)

This subcortical dementia occurred in 15% of AIDS patients prior to the introduction of HAART but the incidence has now been reduced by 50%. Risk factors for the development of HIV-associated dementia (HAD) include: low CD4 counts, increasing age, anaemia, systemic symptoms, injection drug use and female sex. Host genetic factors such as the E4 isoform for apolipoprotein E may also be a predisposing factor. The pathological features of HAD are an HIV encephalitis (HIVE), usually

Table 8.29 Peripheral nerve complications in HIV infection.

HIV related
Axonal neuropathy (distal sensory peripheral neuropathy)
Demyelinating neuropathy (GBS and CIDP)
Vasculitic neuropathy
Diffuse inflammatory lymphocytic syndrome
Lower motor neurone syndrome (resembling MND)
CMV related
Lumbosacral polyradiculopathy
Vasculitic neuropathy
Drugs
Antiretroviral drugs (ddI, ddC, D4T, ?protease inhibitors)
Isoniazid (treatment of TB)
Thalidomide (treatment of mouth ulcers)
Dapsone (treatment and prophylaxis of toxoplasmosis and *Pneumocystis jirovecii*)
Vincristine and vinblastine (treatment of KS and lymphoma)
Paclitaxel (Taxol) (treatment of KS)
Others
Syphilis (polyradiculopathy)
Metastatic NHL
Ganglionitis
Autonomic neuropathy

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CMV, cytomegalovirus; GBS, Guillain–Barré syndrome; KS, Kaposi sarcoma; MND, motor neurone disease; NHL, non-Hodgkin lymphoma; TB, tuberculosis.

at the grey–white interface, suggesting haematogenous dissemination. The hallmark for HIVE is the presence of microglial nodules which are a fusion of HIV infected and non-infected macrophages. Most infection is demonstrated in the basal ganglia, the brainstem and the deep white matter areas. Other pathological features include leuco-encephalopathy and areas of neuronal cell loss, especially in the hippocampal areas and the frontal and temporal lobes. Because neuronal cells are rarely affected, the pathophysiology of HAD probably results from the release of inflammatory cytokines such as tumour necrosis factor, quinolinic acid and platelet-activating factor by activated macrophages.

The clinical features of HAD in the early stages may be mild with symptoms of poor concentration, mental slowing and apathy which may mimic a depressive disorder. Later, as the syndrome progresses, more specific cognitive changes with memory loss and personality change develop. These occur in association with motor changes such as impaired dexterity and gait problems which result from the associated vacuolar myelopathy and peripheral neuropathy. Examination may show impaired pursuit and saccadic eye movements, generalized hyperreflexia, cerebellar and frontal release signs. Investigations are indicated to exclude other causes – MRI typically shows evidence of atrophy with diffuse white matter changes on T2 weighted images. The CSF shows non-specific cytochemical abnormalities but must be examined to exclude conditions such as neurosyphilis, CMV and PML. The CSF viral load correlates with severity of dementia but is not sensitive enough for diagnostic purposes. Formal neuropsychological assessments typically reveal abnormalities in the following cognitive domains – psychomotor speed, attention, frontal lobe function and verbal and non-verbal memory.

Pre-HAART, the mean survival rate for patients with HAD was 12 months. With the introduction of HAART, some patients may improve, some remain static and some with virological non-response may continue to deteriorate. A minority of patients with evidence of viral suppression in the peripheral circulation may continue to deteriorate as a result of 'compartmentalization' with a high viral load in the CSF which will necessitate a change in HAART regimen. There is concern regarding the ability of the currently available antiretroviral drugs to penetrate the blood–brain barrier, particularly the protease inhibitor drugs. The following drugs seem to have the best penetration: stavudine, zidovudine, abacavir, lamivudine, efavirenz, nevirapine and indinavir (Table 8.30). However, to date no one HAART regimen has proved superior to another in the treatment of HAD suggesting that it is the suppression of viral replication in the peripheral circulation that is crucial.

HIV-related vacuolar myelopathy

Clinically significant vacuolar myelopathy affects up to 10% of patients with AIDS usually in patients who also have HAD. The condition is characterized by a slowly progressive spastic paraparesis, sphincter disturbance and a sensory ataxia resulting from posterior column involvement. There is no sensory level. Pathological specimens demonstrate a vacuolar degeneration of the white matter within the thoracic spinal cord similar to that seen in subacute degeneration of the cord resulting from vitamin B_{12} deficency. Although B_{12} levels are usually normal, it is possible that a methylation defect is responsible because S-adenosylmethionine is reduced in the CSF of patients with vacuolar myelopathy. This degeneration is not specific to AIDS and has been described in other immunodeficient states and malignancy. As with the other complications of HIV, significant productive HIV infection is not found. However, there is evidence of macrophage activation and increased levels of cytokines. MRI shows increased signal in the white matter tracts on T2 images or may be normal. CSF examination is necessary to exclude viral myelitis resulting from herpes zoster, herpes simplex and CMV although these myelitides tend to be much more acute. Co-infection with HTLV-1, which has a similar mode of transmission to HIV, merits consideration. There is no specific treatment apart from HAART. A small study using 3 g methionine showed some limited benefit but results of larger studies are awaited.

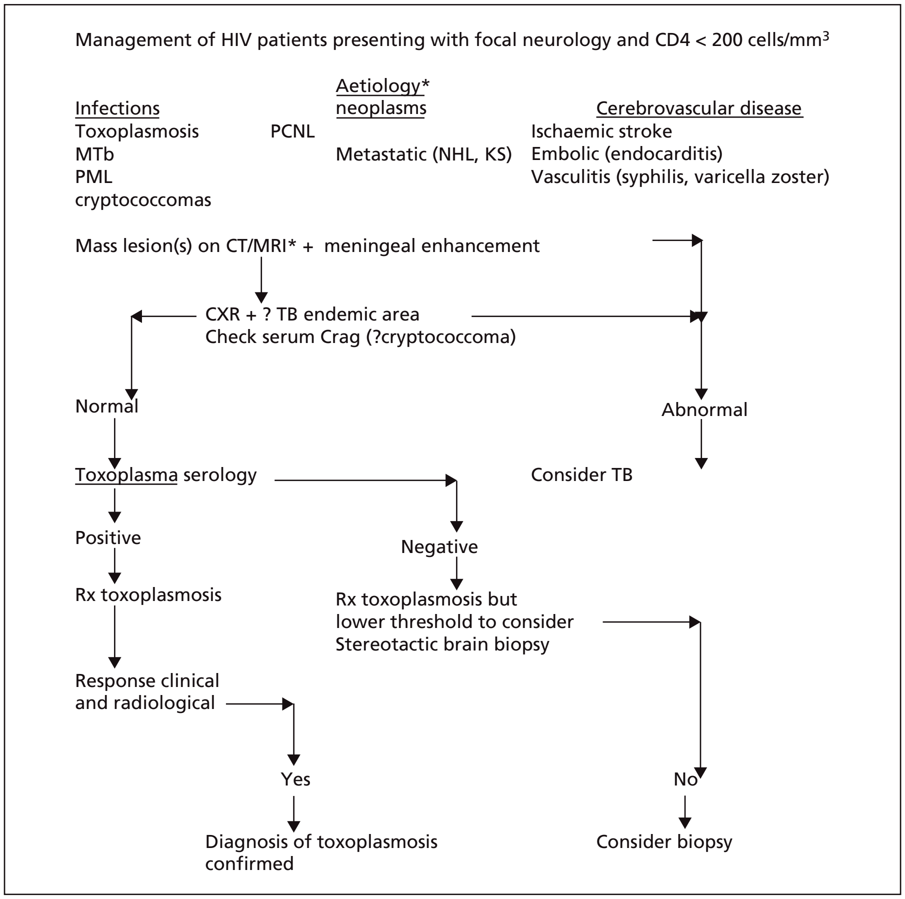
HIV-related neuropathy

The most common peripheral nerve disorder encountered because of HIV is distal sensory peripheral neuropathy (DSPN). The prevalence rate pre-HAART was estimated at 35% and at

Table 8.30 Drug treatment regimens for the common HIV-related CNS infections.

TOXOPLASMOSIS	
Acute phase (for 6 weeks)	**Side effects**
First line therapy	
Pyrimethamine loading dose	Marrow suppression
(100 mg p.o. for 3 days, then 75 mg/day)	
+	
Sulfadiazine 6–8 g/day p.o./iv	Rash
	Nephrotoxicity
+	Marrow suppression
Folinic acid 15 mg/day	
Second line therapy	
Clindamycin 600–900 mg/day p.o./iv instead of sulfadiazine	Rash, diarrhoea
Maintenance treatment*	
Pyrimethamine 25–50 mg/day	
+	
Sulfadiazine 2–4 g/day	
+	
Folinic acid 10 mg/day	
Clindamycin 600 mg/day instead of sulfadiazine	
CRYPTOCOCCAL MENINGITIS	
Acute phase therapy for 4–6 weeks or until CSF culture negative	
Amphotericin B 0.7–1.0 mg/kg/day (via central line)	Nephrotoxicity
+/–	Anaemia, hepatitis
Flucytosine 100–150 mg/kg/day p.o.	Marrow suppression
In milder cases:	
Fluconazole 400 mg iv/p.o.	Rash, hepatitis
*Maintenance treatment**	
Fluconazole 200–400 mg/day p.o.	
CYTOMEGALOVIRUS INFECTION	
Acute phase therapy	
Ganciclovir 5 mg/kg every 12 hours for 14–21 days	Anaemia, leucopenia, thrombocytopenia
or	
Foscarnet 60 mg/kg 8-hourly for 14–21 days	Renal failure
	Leucopenia
Maintaince treatment*	
Ganciclovir 5 mg/kg every 24 hours	
or	
Foscarnet 90–120 mg/kg/day	

Table 8.30 *Continued*


Management of HIV patients presenting with focal neurology and CD4 < 200 cells/mm3
Aetiology*
Infections
neoplasms
Cerebrovascular disease
Toxoplasmosis
PCNL
Ischaemic stroke
MTb
Metastatic (NHL, KS)
Embolic (endocarditis)
PML
Vasculitis (syphilis, varicella zoster)
cryptococcomas
Mass lesion(s) on CT/MRI* + meningeal enhancement
CXR + ? TB endemic area
Check serum Crag (?cryptococcoma)
Normal
Abnormal
Toxoplasma serology
Consider TB
Positive
Negative
Rx toxoplasmosis
Rx toxoplasmosis but
lower threshold to consider
Stereotactic brain biopsy
Response clinical
and radiological
Yes
No
Diagnosis of toxoplasmosis
confirmed
Consider biopsy

CT, computed tomography; CXR, chest X-ray; KS, Kaposi sarcoma; MRI, magnetic resonance imaging; MTb, *Mycobacterium tuberculosis*; NHL, non-Hodgkin lymphoma; PCNL, primary CNS lymphoma; PML, progressive multifocal leucoencephalopathy.

* Consider stopping maintenance treatment if after highly active antiretroviral therapy (HAART) is started the CD4 remains >200 cells/mm^3 for >6 months.

MRI preferred as more sensitive.

If there are signs of raised intracranial pressure, treat with dexamethasone 4 mg q.d.s. initially. Once the patient is stable, gradually tail off. Improvement on steroids may be because of reduction of cerebral oedema or partial response of lymphoma to corticosteroids.

At least 2 weeks may be necessary to assess for a response to anti-*Toxoplasma* therapy. In some cases, if no urgency, monitor for 4 weeks with repeat MRI.

necropsy 95% of patients had sural nerve pathological abnormalities. The underlying pathology in DSPN is one of a dying back axonopathy with secondary demyelination. Increased numbers of macrophages are found in the dorsal root ganglia and within the peripheral nerves. HIV RNA is rarely detected in the peripheral nerves and the pathophysiological mechanisms for the development of DSPN are those for HAD, i.e. neurotoxicity of viral proteins such as Gp 120 and tat as well as a bystander effect of neurotoxic cytokines released by activated macrophages.

Risk factors for the development of DSPN include age, higher viral load and lower CD4 counts. Patients with other risk factors for neuropathy such as diabetes, excess alcohol intake and genetic neuropathies are more vulnerable. The presentation is with 'painful, burning, numb feet'. Patients also complain of paraesthesiae, dysaesthesiae and allodynia but the upper limbs are rarely involved. Examination may reveal limited weakness, often confined to the intrinsic foot muscles. The reflexes may be normal, depressed or absent. There is characteristically impaired sensation to pain and temperature but subsequently other modalities are involved. Nerve conduction tests (NCTs) may be normal or show mild axonal abnormalities. Thermal thresholds are abnormal indicating small fibre involvement. Punch skin biopsies with the assessment of epidermal nerve fibre densities are increasingly being utilizsed in diagnosis and treatment trials of DSPN. In atypical cases where, for example, there is more extensive weakness with foot drop or significant upper limb involvement clinically or on NCTs, CSF examination and nerve biopsy should be considered to exclude vasculitis, demyelinating neuropathies and lymphomatous infiltration.

The treatment of DSPN is symptomatic – only lamotrigine and recombinant human nerve growth factor have been shown to be effective in relieving the pain of DSPN in randomized placebo controlled trials. Gabapentin, although often used, has only been shown to be effective in small trials. Amitriptyline, although not proven to be effective in placebo controlled trials, has a role in individual patients starting at low doses. Mexiletine, acupuncture and topical capsaicin have not shown benefit.

Diffuse inflammatory lymphocytosis syndrome

Some patients respond to HIV infection by developing diffuse inflammatory lymphocytosis syndrome (DILS), a syndrome characterized by a persistent circulating CD8 lymphocytosis with visceral lymphocytic infiltration particularly affecting the salivary glands. An uncommon form of HIV-associated neuropathy is seen in DILS which is eminently treatable with antiretroviral drugs and corticosteroids. This multisystem disorder resembles Sjögren syndrome, although anti-Ro/SS-A and anti-La/SS-B antibodies are absent. Patients present with salivary gland enlargement, xerostomia, keratoconjunctivitis sicca, uveitis and lymphocytic pulmonary, gastrointestinal and renal involvement. The peripheral nerve complications present with a painful sensorimotor neuropathy which may be symmetrical or asymmetrical. Neurophysiological studies show an axonal neuropathy although rare cases of demyelination are reported. The CD4 counts are variable but the CD8 counts are consistently high, resulting in a low CD4 : CD8 ratio. The diagnosis is confirmed at nerve biopsy.

Toxic neuropathy for antiretroviral drugs

The nucleoside reverse transcriptase inhibitors (NRTIs) didanosine (ddI), zalcitabine (ddC) and stavudine (d4T) have all been shown to cause a dose-dependent peripheral neuropathy but an association with lamivudine (3TC) is not well documented. Mitochondrial toxicity from inhibition of the DNA polymerase enzyme may be the underlying mechanism for the neuropathy and the same mechanism may also account for the other side effects of this class of drug – pancreatitis, fulminant hepatic failure, lactic acidosis and lipodystrophy. More recently, protease inhibitors (PI) have also been implicated in the drug-related neuropathies. The clinical presentation of toxic neuropathy for antiretroviral drugs (TNA) is similar to that seen with DSPN. The drug-related neuropathies are, however, more likely to be painful, have an abrupt onset and progress rapidly. After stopping the appropriate drug, there may be a paradoxical worsening of neuropathic symptoms over a period of 4–8 weeks (coasting). An improvement of symptoms may occur in some patients but a number may be left with underlying DSPN which has been unmasked by the TNA.

As with DSPN, the management of this group of patients can be difficult. The development of this painful sensory neuropathy is a significant cause of morbidity and poor drug compliance. If the patient is on a neurotoxic drug, the issue of stopping it needs to be discussed with their HIV physician. In practice, this maybe a difficult decision if there has been a good virological response and the CD4 count has risen significantly as lowering the drug dosage risks the possibility of viral drug resistance. Treatment is otherwise symptomatic. One small study has shown acetylcarnitine improves neuropathic pain scores and epidermal skin nerve fibre densities.

HIV-associated myopathy

An immunologically mediated polymyositis may occur at seroconversion or during the asymptomatic phases of the disease. As with non-HIV patients, the subacute illness manifests with proximal weakness and myalgia, an elevated creatine phosphokinase and myopathic changes on EMG studies. The disorder is usually steroid responsive. The inflammatory infiltrates found on muscle biopsy are similar to HIV – negative polymyositis, except there is a reduction of CD4 positive cells. Zidovudine, an NRTI introduced in 1986, causes a mitochondrial myopathy. Muscle biopsies show ragged red fibres and muscle mitochondrial DNA levels are significantly depleted. Patients improve when the drug is stopped. This complication in now rare since the drug doses have been reduced from 1000–1500 mg/day to 600 mg/day.

Immune reconstitution inflammatory syndrome (IRIS)

A consequence of HAART is that the recovery of CD4 T lymphocytes leads to recovery of memory T cells. This has led to the development of so-called immune restoration or immune reconstituition syndrome. This has been defined as the ‘paradoxical deterioration of clinical or laboratory parameters including imaging studies, despite a favourable response of the HIV surrogate markers, (i.e. viral load and CD4 count) to antiretroviral therapy (ART)’. A total of 10–25% of patients on ART may develop IRIS, which may occur days to months after starting ART but usually within the first 2 months. IRIS maybe subdivided into three categories:

1 Infectious IRIS caused either by ongoing or latent infection.
2 Sarcoid-like IRIS with granulomatous lesions in the lungs.
3 Autoimmune IRIS with patients developing disorders such as SLE, polymyositis and rheumatoid arthritis.

Neurological IRIS has been described with *Mycobacteria tuberculosis* causing meningitis and abcesses; CMV with the development of vitritis, uveitis and cystoid macular oedema; HIV itself has caused a demyelinating leuco-encephalopathy. IRIS-induced cases of PML demonstrate gadolinium enhancement on MRI and, of those cases that have been biopsied, inflammatory infiltrates. The management of IRIS consists of treating any identified infection and corticosteroids for the inflammatory component. The question of whether to stop or continue ART is difficult. If there is a life-threatening complication such as a mass lesion within the brain, it would seem prudent to stop the drugs at least for a short period.

Conclusions

Since the onset of the AIDS epidemic, tremendous strides have been made in unravelling the immunobiology of HIV; the development of the antiretroviral drugs which have made HIV a chronic medical disorder rather than an inexorably fatal one; identifying and treating the opportunistic complications with better diagnostic and therapeutic options. However, these benefits have not to date reached the areas of the world most affected by the epidemic. From the neurology point of view, DSPN continues to pose problems. Although the incidence of HAD has declined, as a result of increased longevity, the prevalence has increased. There is concern from pathological data on patients who have died while on HAART about ongoing low-grade inflammation in the brain. IRIS has also proved difficult to diagnose and manage.

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9 Nerve and Muscle Disease

Michael Lunn, Michael Hanna, Robin Howard, Matthew Parton, Mary Reilly

Neuromuscular diseases have traditionally been overlooked, underdiagnosed and poorly treated when compared with neurological diseases with greater visibility (e.g. Parkinson's disease or epilepsy), social impact (such as the dementias) or which pose a threat for survival (e.g. brain tumours or meningitis). However, neuromuscular disorders are diverse and extremely common, possibly accounting for up to 40% of neurological diagnoses. They may lead to significant disability or death. The accurate and early diagnosis of a cause may lead to effective treatment, reduction in disability and improved quality of life.

This chapter provides a comprehensive summary of disorders of peripheral nerve, neuromuscular junction, muscle and the anterior horn cell.

Peripheral nerve disorders

An understanding of the many peripheral nerve disorders relies upon a comprehension of the complexities of the macro- and micro-anatomy of peripheral nerves, their molecular biology, immunology and pathophysiology. Much of this is beyond the scope of this chapter but a short synopsis is provided below.

Macro-anatomy of the peripheral nerve

Peripheral nerves are bundles of axons, Schwann cells, elaborated myelin and the supporting cellular tissues whose primary purpose is to communicate neural information between the CNS and peripheral sensory or effector structures (e.g. muscles, sweat glands, blood vessels). In very simplified terms, the peripheral nervous system (PNS) functions via a series of reflex arc circuits with efferent and afferent arms controlled from above by the CNS (Figure 9.1).

The anatomy of the major nerve trunks and their connections has been known for more than 500 years, even if there was little understanding of their function (Figure 9.2). The PNS consists of 10 of the 12 cranial nerves and the spinal roots, becoming the peripheral nerves, exiting from the spinal cord. Knowledge of basic peripheral neuroanatomy, physiology and immunology is the key to understanding the pathophysiology of diseases affecting peripheral nerves.

Upper limbs

The brachial plexus is formed from the anterior rami of the spinal roots from C5 to T1 (Figure 9.3). Within the course of the brachial plexus, axons originating from these cervical roots are rearranged and exit in major and minor nerve branches to supply sensory, motor and autonomic inputs and outputs to the upper limb and shoulder girdle (Table 9.1(a); Figure 9.4). Many find the localization of processes affecting the brachial plexus or cervical roots difficult but it is simplified by an understanding of the anatomy. The identification of affected muscle groups and sensory territories assist.

The major nerves leaving the brachial plexus are the musculocutaneous, median, ulnar and radial nerves (see below and Figure 9.4). Each nerve has its innervated muscles (although there are occasional anatomical variations).

Lower limbs

The lumbosacral plexus is formed from the ventral rami of L1–S4 nerve roots (Figure 9.6). The upper (or lumbar) part of the plexus gives rise to the obturator and femoral nerves. The lower part of the plexus gives rise to the sciatic nerve which is regionally organized and later divides into the tibial and common peroneal nerves at the knee. As with the brachial plexus, some smaller nerves exit the plexus directly (e.g. the genitofemoral and lateral cutaneous nerve of the thigh). The major nerves of the lumbosacral plexus innervate individual muscles as indicated in Figure 9.6 (Table 9.1(b)). An ability to identify which muscles or areas of skin innervation are affected on clinical and neurophysiological examination and correlate this to the anatomical innervation is

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Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

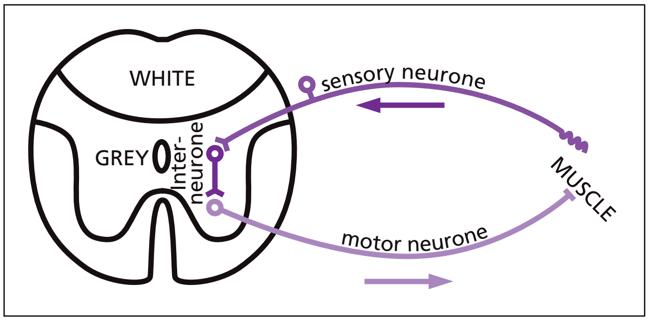
WHITE
GREY
Inter-neurone
sensory neurone
MUSCLE
motor neurone

Figure 9.1 The spinal reflex arc is the foundation of peripheral nerve function. Although highly stylized, peripheral stimuli enter the arc along the afferent limb and exit to effector organs along the efferent limb. Responses may be modified by synaptic connections along this pathway.

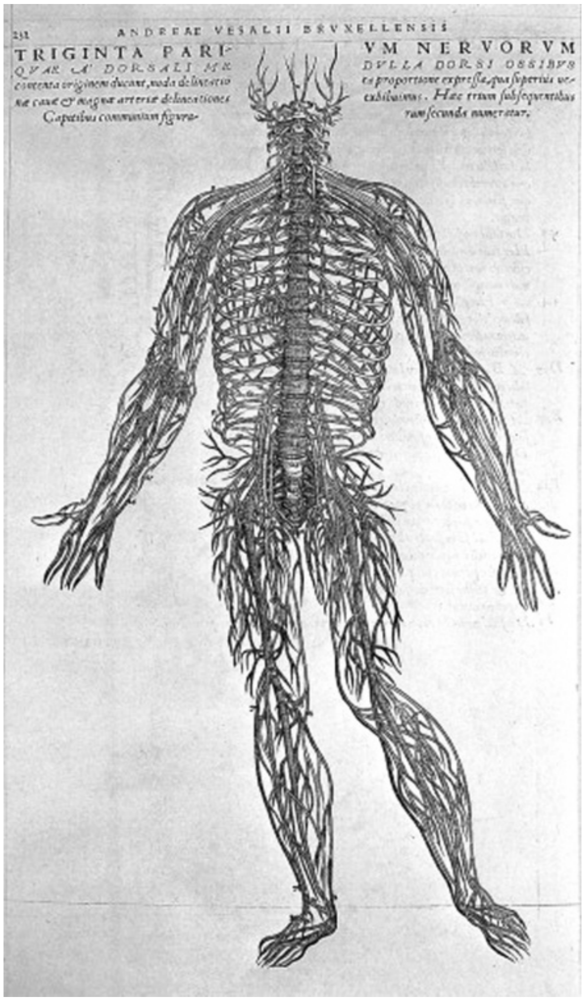
232
ANDREAE VESALII BRVXELLENSIS
TRIGINTA PARI-
VM NERVORVM
QVAE A DORSALI ME-
DVLLA DORSI OSSIBVS

Figure 9.2 Andreas Vesalius (1514–1564) *De humani corporis fabrica*, Basel: Oporinus, 1543. lib. IV, pp. 353–354. Courtesy of the Wellcome Library, London.

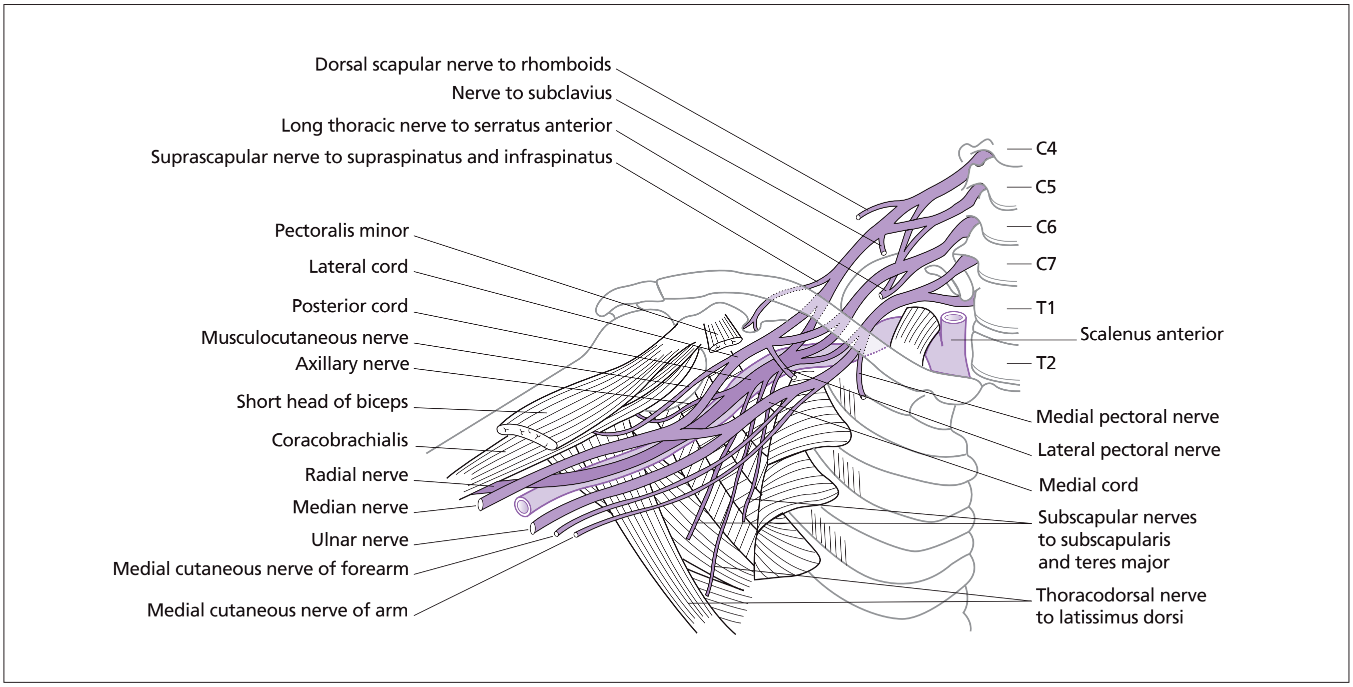
Dorsal scapular nerve to rhomboids
Nerve to subclavius
Long thoracic nerve to serratus anterior
Suprascapular nerve to supraspinatus and infraspinatus
Pectoralis minor
Lateral cord
Posterior cord
Musculocutaneous nerve
Axillary nerve
Short head of biceps
Coracobrachialis
Radial nerve
Median nerve
Ulnar nerve
Medial cutaneous nerve of forearm
Medial cutaneous nerve of arm
C4
C5
C6
C7
T1
Scalenus anterior
T2
Medial pectoral nerve
Lateral pectoral nerve
Medial cord
Subscapular nerves to subscapularis and teres major
Thoracodorsal nerve to latissimus dorsi

Figure 9.3 The brachial plexus, its branches and the muscles that they supply. (From *Aids to the Examination of the Peripheral Nervous System*, 4th edn. London: W.B. Saunders, 2000 with permission, courtesy of Dr M. D O'Brien.)

Table 9.1 (a) Innervations. Upper limb. The bold type indicates the predominant innervation of the muscle where that exists.

	Muscles innervated	Spinal roots
Spinal accessory nerve	Trapezius	C3, C4
Brachial plexus	Rhomboids	C4, C5
	Serratus anterior	C5, C6, C7
	Pectoralis major – clavicular head	**C5**, C6
	Pectoralis major – sternal head	C6, **C7**, C8
	Supraspinatus	**C5**, C6
	Infraspinatus	**C5**, C6
	Latissimus dorsi	C6, **C7**, C8
	Teres major	C5, C6, C7
Axillary nerve	Deltoid	C5, C6
Musculocutaneous nerve	Biceps	C5, C6
	Brachialis	C5, C6
Radial nerve	Triceps (long, lateral and medial head)	C6, C7, C8
	Brachioradialis	C5, C6
	Extensor carpi radialis longus	C5, C6
Posterior interosseous nerve	Supinator	C6, C7
	Extensor carpi ulnaris	**C7**, C8
	Extensor digitorum	**C7**, C8
	Abductor pollicis longus	**C7**, C8
	Extensor pollicis longus	**C7**, C8
	Extensor pollicis brevis	**C7**, C8
	Extensor indicis	**C7**, C8
Median nerve	Pronator teres	C6, C7
	Flexor carpi radialis	C6, C7
	Flexor digitorum superficialis	C7, **C8**, T1
	Abductor pollicis brevis	C8, **T1**
	Flexor pollicis brevis	C8, **T1**
	Opponens pollicis	C8, **T1**
	Lumbricals I & II	C8, **T1**
Anterior interosseous nerve	Pronator quadratus	C7, **C8**
	Flexor digitorum profundus I & II	C7, **C8**
	Flexor pollicis longus	C7, **C8**
Ulnar nerve	Flexor carpi ulnaris	C7, **C8**, T1
	Flexor digitorum profundus III & IV	C7, **C8**
	Hypothenar muscles	C8, **T1**
	Adductor pollicis	C8, **T1**
	Flexor pollicis brevis	C8, **T1**
	Palmar interossei	C8, **T1**
	Dorsal interossei	C8, **T1**
	Lumbricals III & IV	C8, **T1**

Table 9.1 (b) Innervations. Lower limb. The bold type indicates the predominant innervation of the muscle where that exists.

	Muscles innervated	Spinal roots
Femoral nerve	Iliopsoas	**L1, L2**, L3
	Rectus femoris	L2, **L3, L4**
	Vastus lateralis	L2, **L3, L4**
	Vastus intermedius	L2, **L3, L4**
	Vastus medialis	L2, **L3, L4**
Obturator nerve	Adductor longus	**L2, L3**, L4
	Adductor magnus	**L2, L3**, L4
Superior gluteal nerve	Gluteus medius and minimus	**L4, L5**, S1
	Tensor fasciae latae	**L4, L5**, S1
Inferior gluteal nerve	Gluteus maximus	**L5, S1**, S2
Sciatic and tibial nerves	Semi-tendinosus	**L5, S1**, S2
	Biceps	L5, **S1**, S2
	Semi-membranosus	L5, **S1**, S2
	Gastrocnemius	S1, S2
	Soleus	S1, S2
	Tibialis posterior	L4, L5
	Flexor digitorum longus	L5, **S1, S2**
	Abductor hallucis	S1, S2
	Abductor digiti minimi	S1, S2
	Interossei	S1, S2
Sciatic and common peroneal nerves	Tibialis anterior	**L4**, L5
	Extensor digitorum brevis	**L5**, S1
	Extensor hallucis longus	**L5**, S1
	Extensor digitorum brevis	L5, S1
	Peroneus longus	L5, S1
	Peroneus brevis	L5, S1

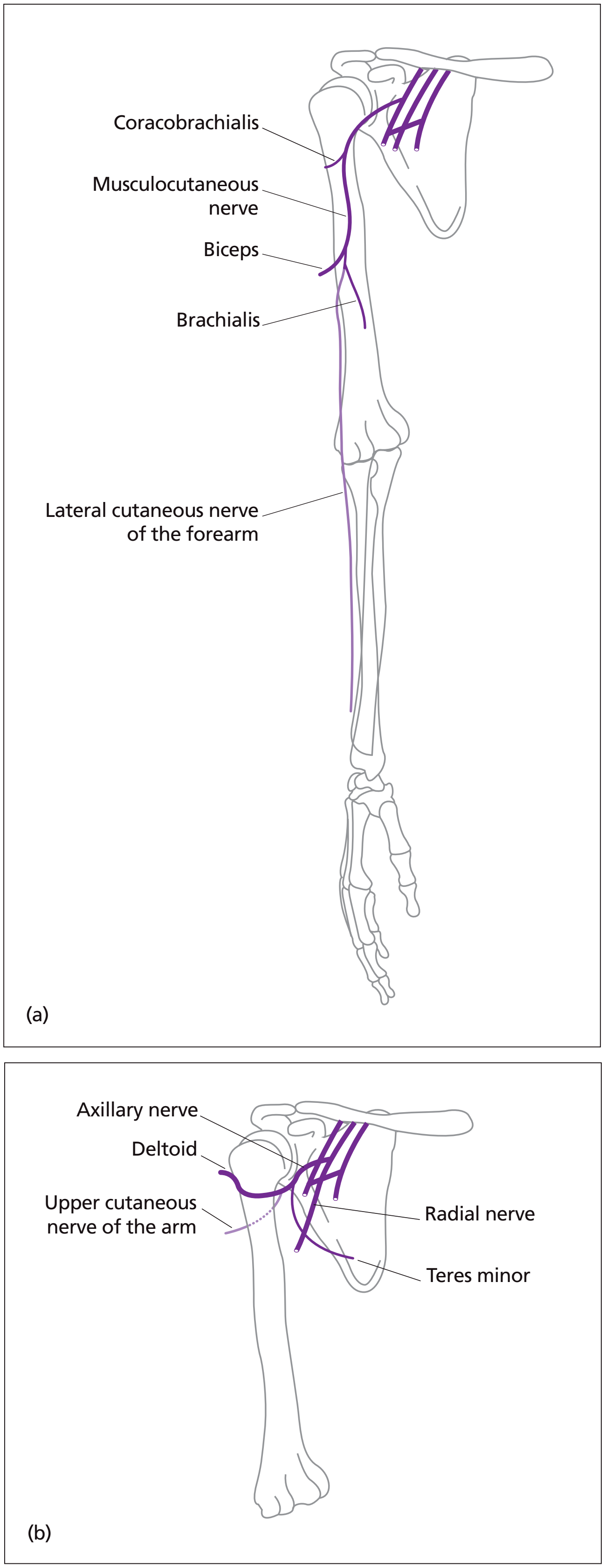
Coracobrachialis
Musculocutaneous nerve
Biceps
Brachialis
Lateral cutaneous nerve of the forearm
(a)
Axillary nerve
Deltoid
Upper cutaneous nerve of the arm
Radial nerve
Teres minor
(b)

Figure 9.4 Nerves of the upper limb, major cutaneous branches and muscles supplied. (a) Musculocutaneous nerve. (b) Axillary nerve.

]

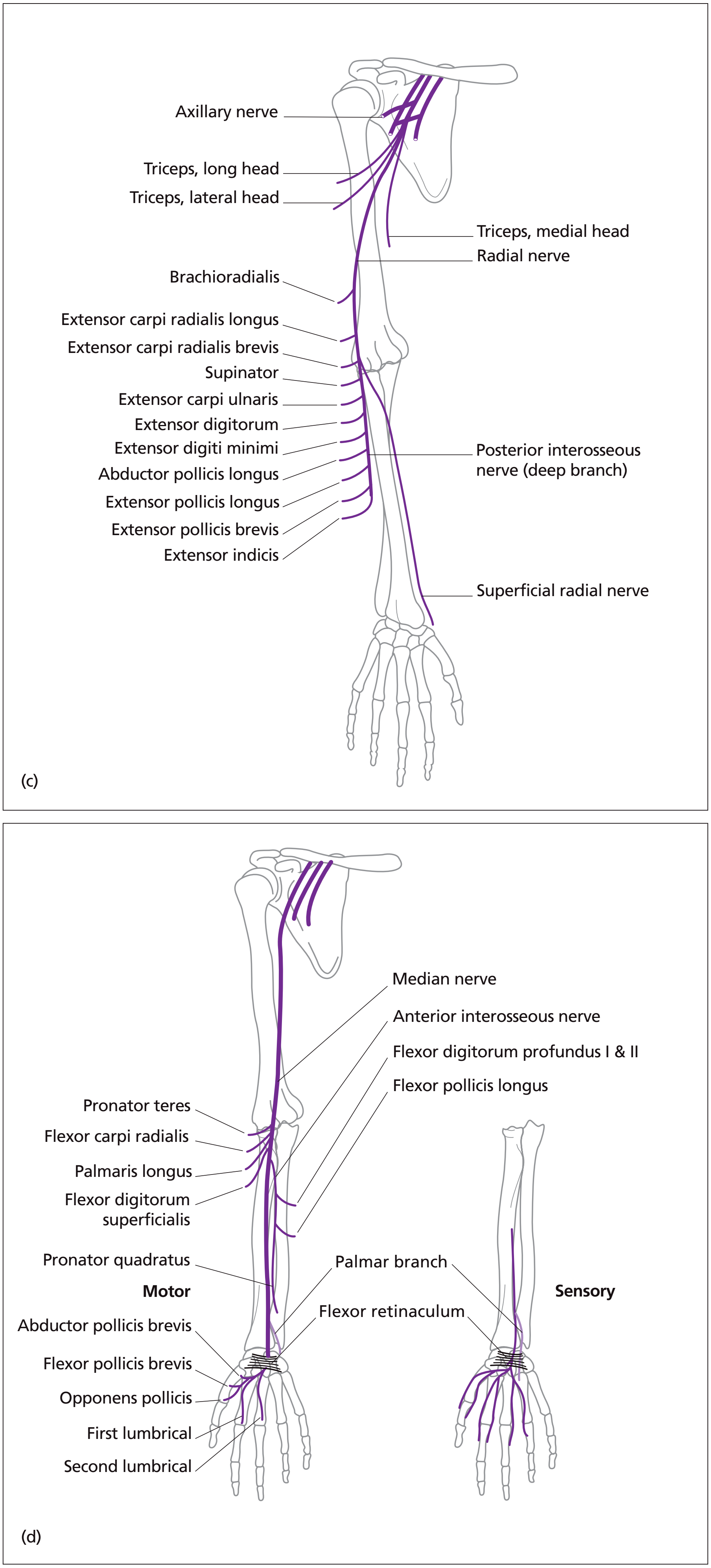
Axillary nerve
Triceps, long head
Triceps, lateral head
Triceps, medial head
Radial nerve
Brachioradialis
Extensor carpi radialis longus
Extensor carpi radialis brevis
Supinator
Extensor carpi ulnaris
Extensor digitorum
Extensor digiti minimi
Abductor pollicis longus
Extensor pollicis longus
Extensor pollicis brevis
Extensor indicis
Posterior interosseous nerve (deep branch)
Superficial radial nerve
(c)
Median nerve
Anterior interosseous nerve
Flexor digitorum profundus I & II
Flexor pollicis longus
Pronator teres
Flexor carpi radialis
Palmaris longus
Flexor digitorum superficialis
Pronator quadratus
Palmar branch
Motor
Sensory
Flexor retinaculum
Abductor pollicis brevis
Flexor pollicis brevis
Opponens pollicis
First lumbrical
Second lumbrical
(d)

Figure 9.4 *Continued* (c) Radial nerve. (d) Median nerve.

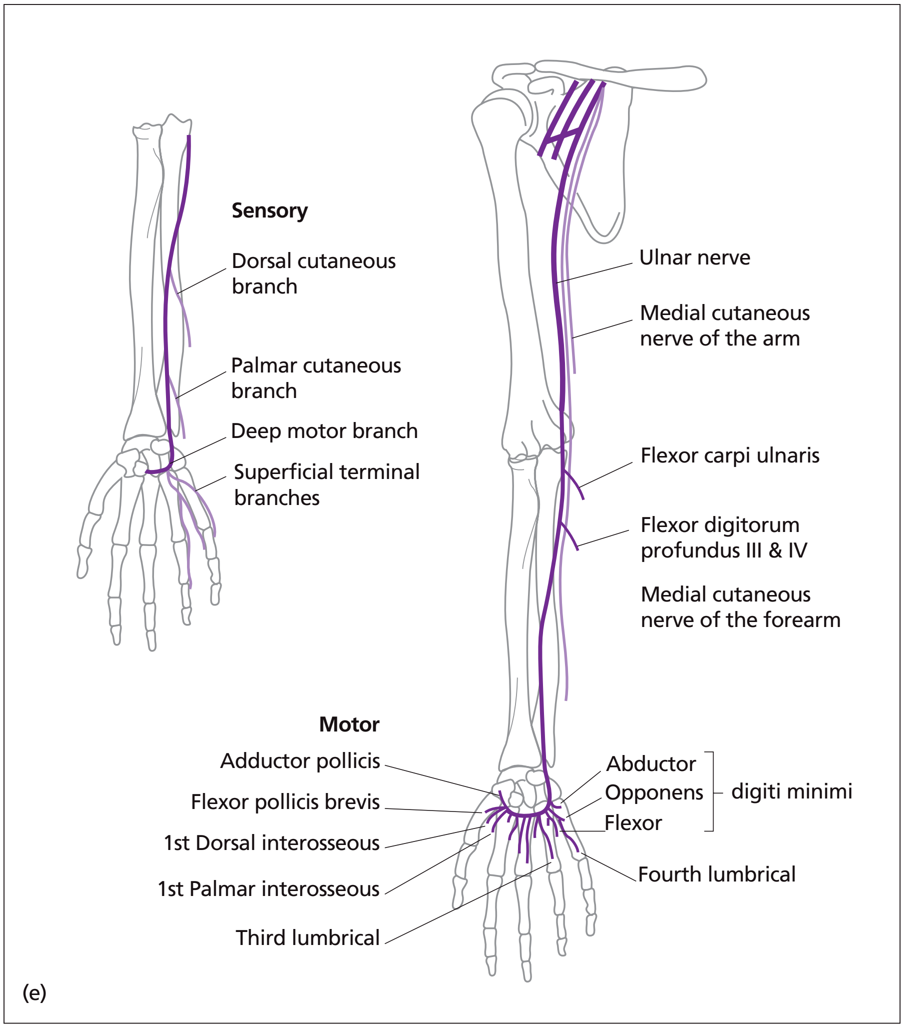
Sensory
Dorsal cutaneous branch
Palmar cutaneous branch
Deep motor branch
Superficial terminal branches
Ulnar nerve
Medial cutaneous nerve of the arm
Flexor carpi ulnaris
Flexor digitorum profundus III & IV
Medial cutaneous nerve of the forearm
Motor
Adductor pollicis
Flexor pollicis brevis
1st Dorsal interosseous
1st Palmar interosseous
Third lumbrical
Abductor
Opponens
Flexor
digiti minimi
Fourth lumbrical
(e)

Figure 9.4 *Continued* (e) Ulnar nerve. (From *Aids to the Examination of the Peripheral Nervous System*, 4th edn. London: W.B. Saunders, 2000 with permission, courtesy of Dr M. D. O'Brien.)

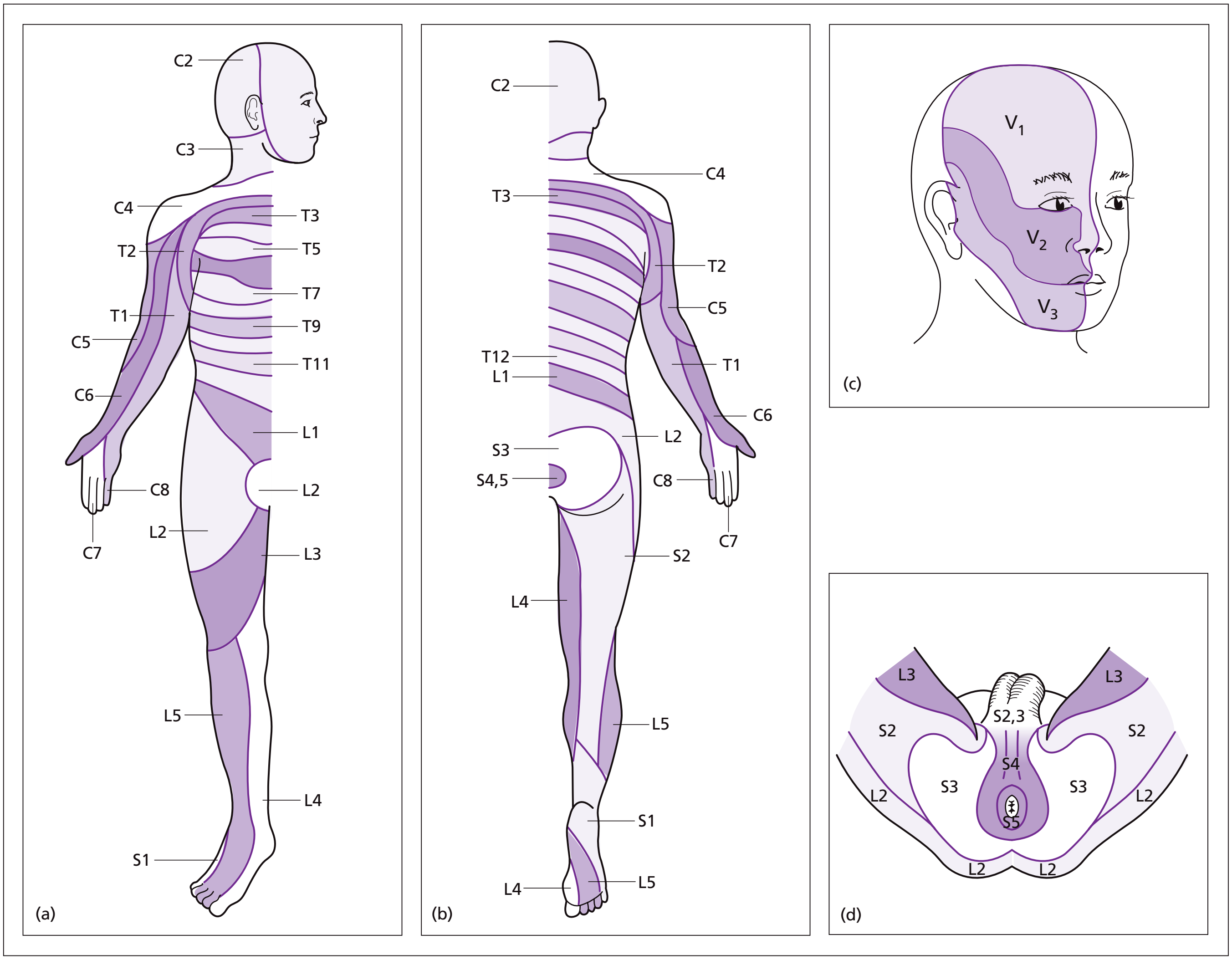
C2
C3
C4
T3
T2
T5
T7
T1
T9
C5
T11
C6
L1
C8
L2
C7
L2
L3
L5
L4
S1
(a)
C2
C4
T3
T2
C5
T12
L1
T1
C6
L2
S3
S4,5
C8
C7
S2
L4
L5
S1
L5
L4
(b)
V1
V2
V3
(c)
L3
L3
S2,3
S2
S2
S4
S3
S3
L2
L2
S5
L2
L2
(d)

Figure 9.5 (a), (b) and (d) Spinal dermatomes. (From *Aids to the Examination of the Peripheral Nervous System*, 4th edn. London: W.B. Saunders, 2000 with permission, courtesy of Dr M. D. O'Brien.) (c) Cutaneous distributions of divisions of Vth nerve. (From Patten 1996, with permission.) Precise distribution varies amongst published sources, especially for sacral dermatomes, perineum and Vth nerve.

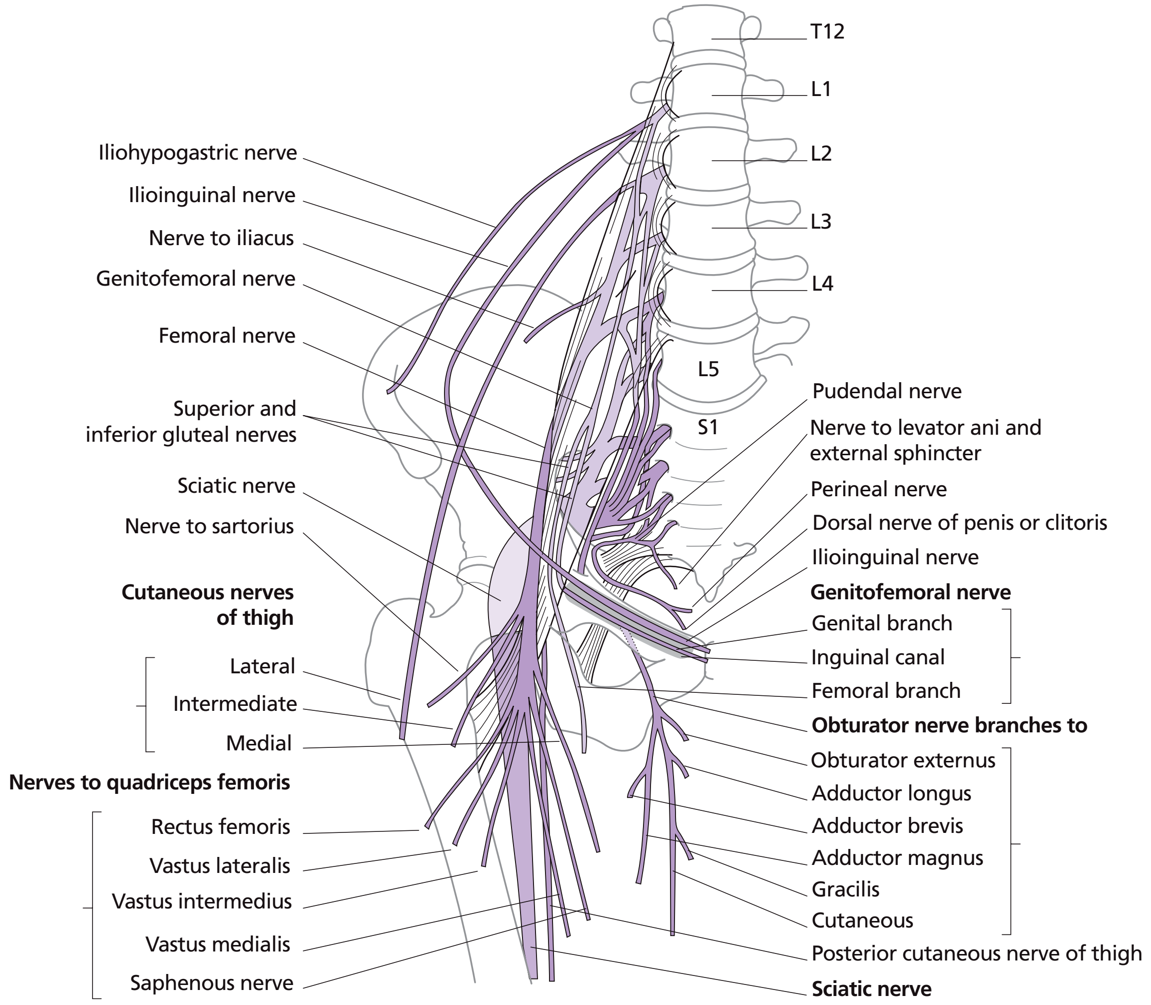
T12
L1
L2
L3
L4
L5
S1
Iliohypogastric nerve
Ilioinguinal nerve
Nerve to iliacus
Genitofemoral nerve
Femoral nerve
Superior and inferior gluteal nerves
Sciatic nerve
Nerve to sartorius
Cutaneous nerves of thigh
Lateral
Intermediate
Medial
Nerves to quadriceps femoris
Rectus femoris
Vastus lateralis
Vastus intermedius
Vastus medialis
Saphenous nerve
Pudendal nerve
Nerve to levator ani and external sphincter
Perineal nerve
Dorsal nerve of penis or clitoris
Ilioinguinal nerve
Genitofemoral nerve
Genital branch
Inguinal canal
Femoral branch
Obturator nerve branches to
Obturator externus
Adductor longus
Adductor brevis
Adductor magnus
Gracilis
Cutaneous
Posterior cutaneous nerve of thigh
Sciatic nerve

Figure 9.6 Lumbosacral plexus, its branches and the muscles that they supply. (From *Aids to the Examination of the Peripheral Nervous System*, 4th edn. London: W.B. Saunders, 2000 with permission, courtesy of Dr M. D. O'Brien.)

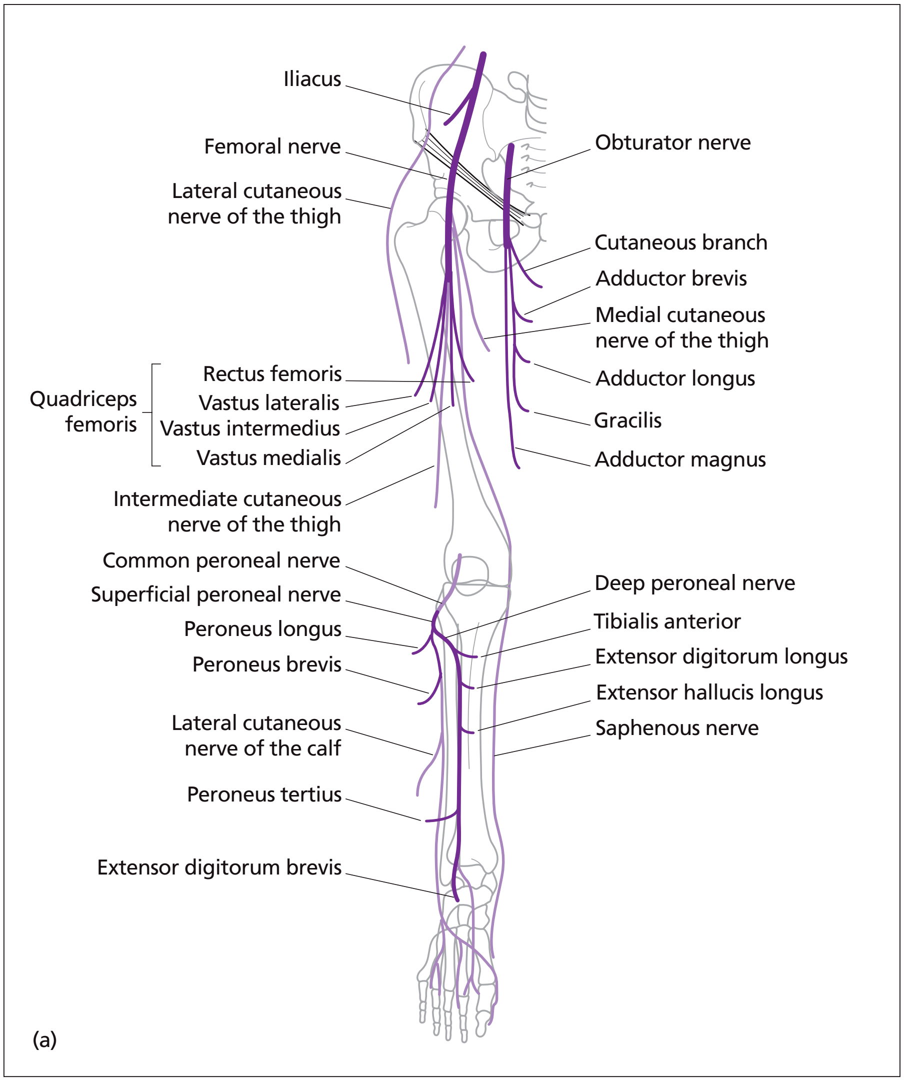
Iliacus
Femoral nerve
Lateral cutaneous nerve of the thigh
Quadriceps femoris
Rectus femoris
Vastus lateralis
Vastus intermedius
Vastus medialis
Intermediate cutaneous nerve of the thigh
Common peroneal nerve
Superficial peroneal nerve
Peroneus longus
Peroneus brevis
Lateral cutaneous nerve of the calf
Peroneus tertius
Extensor digitorum brevis
Obturator nerve
Cutaneous branch
Adductor brevis
Medial cutaneous nerve of the thigh
Adductor longus
Gracilis
Adductor magnus
Deep peroneal nerve
Tibialis anterior
Extensor digitorum longus
Extensor hallucis longus
Saphenous nerve
(a)

Figure 9.7 Nerves of the lower limb, major cutaneous branches and muscles supplied. (a) Anterior aspect.

central to being able to make successful peripheral nerve diagnoses (Figures 9.5 and 9.7).

Micro-anatomy of the peripheral nerve

Each peripheral nerve comprises a collection of neurones and their bundles of axonal processes, supporting cells, blood vessels, connective tissue and other elements including cells of the immune system (e.g. macrophages and mast cells). An axon and its supporting cells (an axon–Schwann cell unit) are often referred to as nerve fibre. A fascicle is a group of nerve fibres with associated endoneurial elements enclosed in ensheathing perineurium. A nerve is a collection of fascicles surrounded by supportive and protective epineurium. Apart from post-ganglionic neurones of the autonomic nervous system, all PNS axons have a CNS extension or origin where the axonal and support matrix characteristics are different.

Peripheral nerve compartments

The peripheral nerve is divided into distinct compartments easily visible when cross-sectioned nerves are examined under the light microscope (Figure 9.8). The compartmentalization of the peripheral nerve provides several layers of protection able to resist physical and immunological attack. Axons are protected from most immune reactions that might otherwise interfere with effective electrical impulse transmission.

The outer layer of epineurium is composed of loosely packed collagenous connective tissue containing adipocytes, fibroblasts, collagen and mast cells and serves to provide tensile strength and resist impact and trauma. The perineurium is a tight sleeve of flattened cells separated by collagen within the epineurium, and surrounds each individual nerve fascicle. The specialized flattened fibroblasts, connected by occlusive tight junctions, form

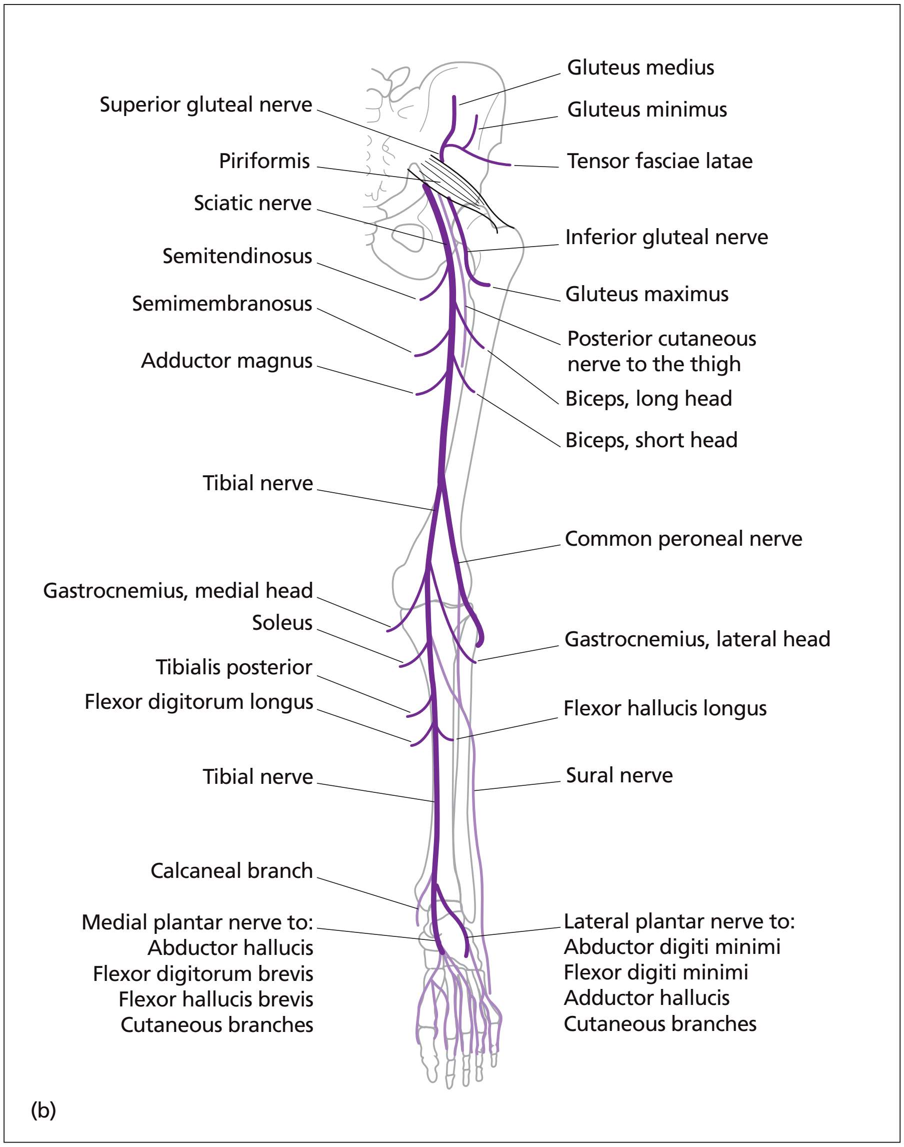
Gluteus medius
Superior gluteal nerve
Gluteus minimus
Tensor fasciae latae
Piriformis
Sciatic nerve
Inferior gluteal nerve
Semitendinosus
Gluteus maximus
Semimembranosus
Posterior cutaneous nerve to the thigh
Adductor magnus
Biceps, long head
Biceps, short head
Tibial nerve
Common peroneal nerve
Gastrocnemius, medial head
Soleus
Gastrocnemius, lateral head
Tibialis posterior
Flexor digitorum longus
Flexor hallucis longus
Tibial nerve
Sural nerve
Calcaneal branch
Medial plantar nerve to:
Abductor hallucis
Flexor digitorum brevis
Flexor hallucis brevis
Cutaneous branches
Lateral plantar nerve to:
Abductor digiti minimi
Flexor digiti minimi
Adductor hallucis
Cutaneous branches
(b)

Figure 9.7 *Continued* (b) Posterior aspect of the lower limb. (From *Aids to the Examination of the Peripheral Nervous System*, 4th edn. London: W.B. Saunders, 2000 with permission, courtesy of Dr M. D. O'Brien.)

an effective barrier to diffusion of macromolecules between the epineurium and endoneurium.

The endoneurium is a tissue space containing connective tissue, axon–Schwann cell units, pericytes, fibroblasts, macrophages and mast cells. The blood vessels in the endoneurium have a specialized endothelium also impermeable to macromolecules. There is no endoneurial lymphatic drainage. The endoneurial space is bathed in endoneurial fluid, the composition of which betrays the specialized protection afforded to this space. The electrolyte composition is that of extracellular fluid to enable electrical nerve conduction but the protein and immunoglobulin content is some 250 times less than that found extracellularly. The fluid is under positive pressure. This unique set of characteristics is possible because the perineurium and the specialized endoneurial endothelium form a blood–nerve barrier (BNB) that is relatively impenetrable to cells and macromolecules under normal conditions. Any active transcellular traffic of essential substances through the perineurium and into the endoneurium probably occurs in pinocytotic vesicles.

Immunology

The peripheral nerves are isolated behind the BNB which provides relative protection from circulating immune factors and perturbations of homeostasis. Not only is the endoneurium physically protected from outside attack, but it is also relatively deficient in the immunological machinery with which to make an internal immunological response. A few macrophages constitutively displaying major histocompatibility complex

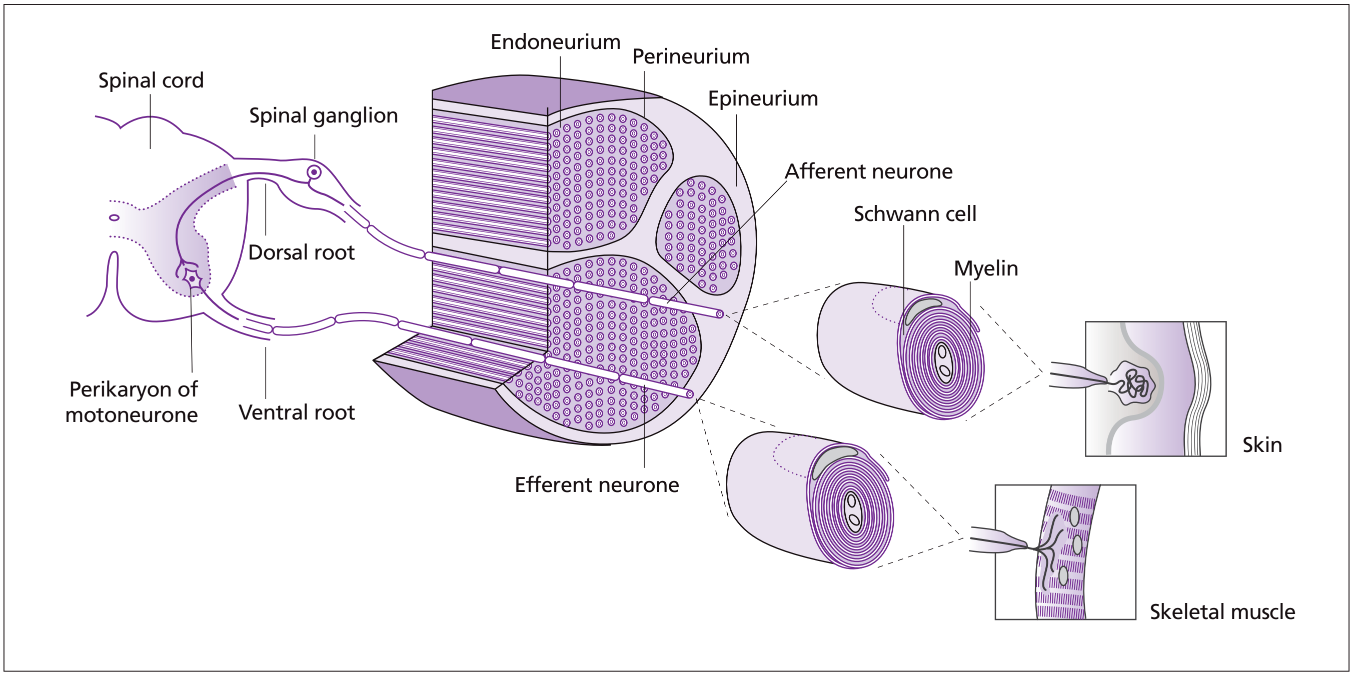

Figure 9.8 Cross-section of a normal nerve. Axons are associated with Schwann cells which in some cases elaborate myelin. Neurones are gathered in fascicles limited by a peri-neurial sheath. The endoneurium also contains supporting stromal cells, endoneurial vessels and, in health, low numbers of immune cells including resident macrophages and mast cells. Fascicles are grouped into nerves limited by the epineurium.

(MHC) Class II are found within the endoneurium and Schwann cells do not usually express MHC markers. Only very limited T-cell traffic occurs into and out of the endoneurium under normal conditions. Restricted access and egress of cells and molecules, raised endoneurial pressure, low constitutive MHC expression and limited patrol by cells of the immune system all contribute to antigen sequestration in the PNS and the relative BNB.

The physical characteristics of the BNB are not the same throughout the PNS. The barrier is relatively deficient at the trigeminal and dorsal root ganglia (DRG), the motor nerve terminals and the sensory endings. MHC Class II expression is up-regulated at the DRG as a result of continuous immune stimulation because of the physical deficiency and the need to patrol more effectively for invading pathogens. In some neuropathies these are the preferred sites for immune attack and development of pathology.

Pathophysiology of the peripheral nerve

All PNS axons are ensheathed by Schwann cells and the Schwann cells are, in turn, invested by a continuous layer of basal lamina. Schwann cells surrounding smaller axons (0.5–1.5 μm) do not elaborate myelin and one Schwann cell may surround several unmyelinated fibres (a Remak bundle). Those surrounding axons of larger calibre (1–20 μm) wrap a single axon only and form a tightly compacted multi-lamellar myelin sheath. Myelin is a lipid-rich specialized extension of the Schwann cell membrane in the PNS (and of oligodendrocytes in the CNS). Although broadly similar in structure, PNS differs from CNS myelin in its molecular composition (Chapter 2).

The pathophysiological mechanisms that result in peripheral neuropathies are almost as diverse as the number of peripheral nerve diagnoses. However, the patterns of damage at a microscopic level are few. Axonal degeneration occurs distal to a site of nerve transection (which may be physical, inflammatory or vascular; and focal, multifocal or diffuse). Axonal degeneration can also occur as a distal dying back phenomenon especially in toxic and metabolic neuropathies. In many inflammatory neuropathies segmental demyelination occurs which may result in conduction failure but not necessarily subsequent axonal degeneration. Remyelination (with thin myelin, short internodes and onion bulbs) may occur, restoring adequate clinical nerve function. Axonal regeneration occurs less consistently and over distances of centimetres only.

Diseases of the peripheral nerve

Diseases of the peripheral nerve can be genetic or acquired. The acquired neuropathies may be primary or secondary to other conditions. The initial clinical approach is similar in all peripheral nerve disorders.

General approach to peripheral nerve disease

History

Patients with peripheral nerve disease complain of sensory disturbance, muscle weakness or wasting (and sometimes fasciculation) and/or symptoms referable to the autonomic nervous system.

Sensory disturbance may be numbness or hypoaesthesia (a term that does not have a correlate in many languages), pain, pins and needles (parasthesiae), heightened sensation (hyperaesthesia), prolonged painful responses (hyperpathia) or abnormal unpleasant sensations perceived from innocuous stimuli (allodynia) or combinations (e.g. a 'painful numbness'). Abnormal sensations are often described in colourful terminology such as like walking on shards of broken glass or sponges or as if limbs were wrapped in cotton wool, hot boots or gripped in a vice. Pain may have a number of qualities that can help the physician. For example, lancinating or shooting pain often associates with large fibre involvement and in the context of an apparent inherited neuropathy may suggest an abnormality in the *SPTLC-I* gene (see below). Burning or stinging pain associates with small fibre involvement. The site of onset and subsequent progression help to differentiate the length dependent sensory neuropathy from the patchy multiple mononeuropathy or dermatomal radiculopathy.

Weakness may be described in terms of handicaps ('I can no longer run for a bus' or 'I can no longer do up my zip fastener') or disability ('My foot flaps' or 'I cannot lift my arms'). The pattern of such deficits helps to point to polyneuropathy, multiple mononeuropathies or radicular involvement. Weakness should always be differentiated from fatigue.

Autonomic disturbances may be missed through lack of recognition of their importance (diarrhoea or bladder dysfunction) or social embarrassment (impotence) by the patient, only compounded by a doctor's unwillingness to enquire. More than infrequent postural hypotension with presyncope or syncope is seldom innocuous. Nocturnal diarrhoea, urinary hesitancy or urgency, impotence and reduced sweating or tearing often require a proactive line of questioning and should be taken seriously if answered in the affirmative.

The tempo of symptom onset is definitive in some conditions and highly useful in the diagnosis of others. In the inflammatory neuropathies accurate determination of the time to the nadir of a first episode distinguishes between Guillain–Barré syndrome (GBS), subacute and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and subsequently determines the selection of treatment. Likewise, a progressive sensory neuropathy with autonomic involvement that has evolved over 7 years is unlikely to be amyloid or paraneoplasia. Furthermore, relapses and remissions (whether spontaneous or following treatment) may favour one diagnosis over another (e.g. CIDP over GBS or an inflammatory neuropathy over a metabolic cause).

The pattern of weakness or sensory loss is a clue to the site of pathology and often to a pathogenic mechanism. Establish the pattern as symmetrical, asymmetrical, focal, multifocal, monomelic or upper or lower limb predominant and any transition from one to another (e.g. multi-focal to symmetrical in vasculitides).

Cranial nerve involvement is important to identify as some conditions have a predilection for one or more cranial nerves (e.g. sarcoidosis and Sjögren's syndrome). Phrenic nerve and diaphragmatic involvement may be disclosed with a history of orthopnoea, early morning headaches or daytime somnolence. A failure to recognize this may lead to a silent and unnecessary death.

Parts of the history, which at first sight may not seem relevant either to the patient or the doctor, are sometimes more important than the reported symptom complex itself. Other concurrent or previous diseases should not necessarily be assumed at face value and should be chased down and checked. For example, a diagnosis of 'asthma', so often reported, when established as relatively recent in an older person may give the clue to Churg–Strauss syndrome or if misattributed to lung disease may give the clue to cardiac involvement in amyloidosis.

An extensive multi-generational family history including details such as consanguinity, non-paternity, early infant death or adoption is crucial to identifying reduced penetrance or recessive disorders. In genetic disorders, careful probing of early and developmental history will often establish a relevant history of symptoms pre-dating the apparent onset of the condition (lack of interest in sport or numbness of the feet after wearing high heels) by a decade or more.

In all situations, exposures to other agents through sex, travel, insect, animal, toxin or drug exposures, should be sought. A systematic and thorough search for other systemic clues should be made, enquiring about skin and nails, joints, sicca symptoms, weight loss and appetite, masses, eyes and other body systems not covered by previous enquiry.

Examination

On inspection the examiner is looking for classic deformities such as pes cavus (Figure 9.9) or other indicators of diagnosis such as amputations, ulceration, wasting (or prominent lack of wasting in conditions with conduction block), trophic skin changes and fasciculations. Tremor occurs in demyelinating disease. Thickened nerves (Figure 9.10; Table 9.2) may be visible, but should be sought and palpated for. Common sites are the ulnar, superficial radial, greater auricular, sural and peroneal.

Examination of the gait can identify both subtle abnormalities of the PNS such as mild distal weakness, or associated features (e.g. ataxia or dystonias). Romberg's sign is of limited use but may be illuminating in sensory neuronopathies. Tone is usually normal or apparently 'reduced'. A careful and correctly performed quantitative motor examination (see O'Brien, *Aids to the Examination of the Peripheral Nervous System,* 2000) is crucial to identify the pattern of root, plexus, nerve or muscle and CNS involvement. Some neuropathies are predominantly or entirely motor (Table 9.3) but most will involve both motor and sensory modalities. Reflex loss may be variable and may evolve (e.g. GBS). Careful documentation of sensory loss in each modality using

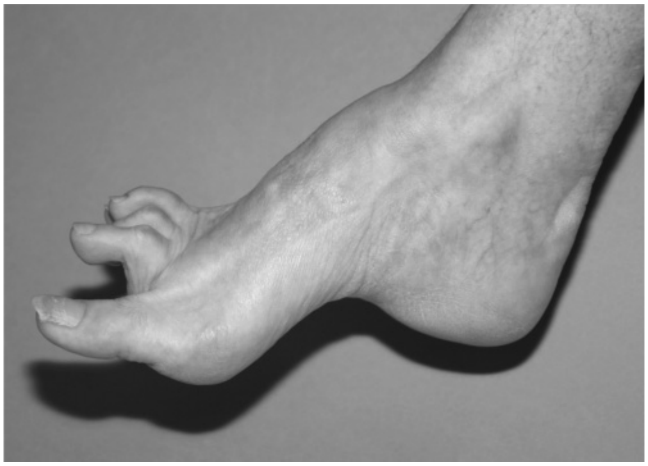

Figure 9.9 The typical lower limb appearances of CMT1A with distal wasting, pes cavus and clawed toes.

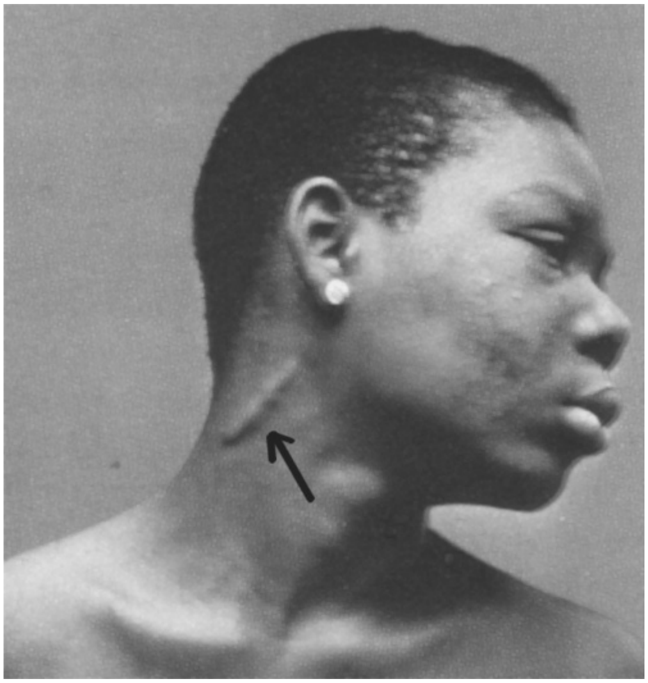

Figure 9.10 Great auricular nerve thickening in leprosy. (From Forbes CD, Jackson WF. *A Color Atlas and Text of Clinical Medicine*. Aylesbury: Wolfe Publishing, 1993, with permission from Elsevier.)

vibration, proprioception, pain, temperature or tickle and light touch may again illuminate disease patterns and pathogenesis. These may be the only findings in some purely sensory neuropathies (Table 9.4).

A subsequent general examination should be thorough but tailored and include close inspection of fundi, skin, nails, joints, testes, breasts and a search for palpable nodes or organomegaly as well as a structured systems examination.

Table 9.2 Causes of thickened nerves.

Hypertrophic Charcot–Marie–Tooth diseases (especially CMT1A and HNPP)
CIDP
Neurofibromatosis
Refsum's disease
Leprosy
Infiltration (lymphoma/secondary deposits)
Amyloidosis
Acromegaly
Perineuroma and other rare primary tumours

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CMT1A, Charcot–Marie–Tooth disease type 1A; HNPP, hereditary neuropathy with liability to pressure palsies.

Table 9.3 Motor neuropathies.

Inherited

- Distal hereditary motor neuropathies
- Spinal muscular atrophy
  - *SMN*: chromosome 5q; recessive
  - Bulbo-spinal muscular atrophies (Kennedy X-linked, recessive, dominant)
  - Tay–Sachs (hexosaminidase A deficiency): chromosome 15; recessive

Acquired

- Motor neurone disease (progressive muscular atrophy) – sporadic/hereditary
- Monomelic atrophy (Hirayama) and other idiopathic focal motor neurone disorders
- Inflammatory
  - Acute motor axonal neuropathy
  - Multifocal motor neuropathy with conduction block
  - Distal lower motor neuropathy associated with anti-GM1 IgM paraprotein
  - Paraneoplastic motor neuropathy (breast/lymphoma)
  - Brachial amyotrophy
- Metabolic and medical
  - Diabetic amyotrophy
  - Porphyria
  - Post-asthmatic amyotrophy (Hopkins syndrome)
- Infective
  - Poliomyelitis, West Nile virus, Central European encephalitis
- Toxins
  - Lead, dapsone, botulism, tick paralysis
- Compressive neuropathies (motor branches)

Differential diagnoses

- Neuromuscular junction disorders: myasthenia gravis, Lambert–Eaton myasthenic syndrome
- Myopathies: distal myopathies; myotonic dystrophy; inclusion body myositis

Scores

The quantification of the examination findings by their incorporation or translation into one of the many available scoring systems is useful for documenting levels of impairment, disability and handicap at a point in time and following patients over the course of their disease or treatment. The use of standardized and validated scales is also useful in combining and comparing data in clinical trials. Commonly used scales are the MRC Scale (for assessment of power, Chapter 3), the Overall Neuropathy Limitation Score, the Modified Rankin Scale, the 10-metre walk time, the Walk-12 and the SF36.

Neurophysiology

A neurophysiological examination should be regarded as an extension of the clinical examination. If it is not performed by the examining physician then it should be performed with detailed communication between the two practitioners to ensure that problems and specific issues can be addressed and clarified. Conduction block may be particularly difficult to identify.

Nerve biopsy

A nerve biopsy should be sought only after careful consideration of the other options available to achieve a diagnosis. Biopsies are generally of sensory nerves, and usually a sensory nerve identifiably and recently affected; a neurophysiologically normal nerve should not be biopsied. The biopsy should be performed with informed patient consent; complications, especially of biopsy site pain, are not infrequent. The nerve biopsy should be performed by someone competent and experienced, as crush or diathermy artefact is easily caused and may render the biopsy uninterpretable. At least 4 cm should be excised for examination.

Table 9.4 Sensory predominant neuropathies.

Inherited
- Hereditary sensory and autonomic neuropathies
- Acute intermittent porphyria
- Fabry's disease

Acquired
- Neuronopathies
  - Paraneoplastic (anti-Hu)
  - Sjögren's syndrome
  - Toxic (pyridoxine, *cis*-platinum)
  - HIV
  - Idiopathic inflammatory
  - Copper deficiency
- Metabolic and deficiency states
  - Diabetic
  - Renal failure
  - Thiamine deficiency, pellagra, Cuban neuropathy (Strachan syndrome)
- Toxins
  - Alcohol, chemotherapy agents (especially platinums), metronidazole, nitrofurantoin, thalidomide, thallium, mercury, phenytoin
- Infectious agents
  - Herpes zoster
  - HIV
  - Leprosy
- Focal compressive (e.g. meralgia paraesthetica, plantar nerves)
- Small fibre neuropathies
- Idiopathic distal sensory axonal neuropathy
- Others: myelopathies, tabes dorsalis, B_{12} deficiency

Staining and examination should again be carried out in consultation with a trained nerve histopathologist. Generic and specific tincturic and immunohistochemical stains can be used to identify or exclude suspected pathologies and special preparation of parts of the specimen for electron microscopy or teased fibre studies should be requested and discussed beforehand.

Inherited neuropathies

The inherited neuropathies can be divided into those in which the neuropathy is the sole or primary part of the disease and those in which the neuropathy is part of a more widespread neurological or multi-system disorder (Table 9.5). The first group includes Charcot–Marie–Tooth disease (CMT). CMT is the most common inherited neuropathy affecting approximately 1/2500 in the Caucasian population, and usually presents with a length dependent sensory motor neuropathy. Most of the other neuropathies in this group are either genetically related to CMT (e.g. hereditary neuropathy with liability to pressure palsies) or can present in a similar fashion (e.g. hereditary sensory and autonomic

Table 9.5 Classification of the inherited neuropathies.

Neuropathies in which the neuropathy is the sole or primary part of the disease
- Charcot–Marie–Tooth disease
- Hereditary neuropathy with liability to pressure palsies
- Hereditary sensory and autonomic neuropathy
- Distal hereditary motor neuropathy
- Hereditary neuralgic amyotrophy
- Familial amyloid polyneuropathy

Neuropathies in which the neuropathy is part of a more widespread neurological or multi-system disorder
- Disturbances of lipid metabolism, e.g.
  - Leuco-dystrophies
  - Lipoprotein deficiencies
  - Phytanic acid storage diseases
  - α-Galactosidase deficiency
  - Cerebrotendinous xanthomatosis
- Porphyrias, e.g.
  - Acute intermittent
  - Hereditary coproporphyria
  - Variegate
  - Amino lavulinic acid dehydrase deficiency
- Disorders with defective DNA, e.g.
  - Ataxia telangiectasia
  - Xeroderma pigmentosum
  - Cockayne's syndrome
- Neuropathies associated with mitochondrial diseases
- Neuropathies associated with hereditary ataxias, e.g.
  - Friedreich's ataxia
  - Spinocerebellar ataxias
- Miscellaneous

neuropathy [HSAN] and distal hereditary motor neuropathy [dHMN]). This group also includes hereditary neuralgic amyotrophy (HNA) which presents with recurrent brachial plexus lesions and familial amyloid polyneuropathy (FAP), a disease in which neuropathy (often including autonomic neuropathy) is the cardinal feature although other systems can be involved (e.g. heart).

The second group is a very large varied group of disorders that usually also involve the CNS (e.g. leucodystrophies, spinocerebellar ataxias) or where systems other than the nervous system are significantly involved (e.g. mitochondrial disorders and porphyrias). Many of these disorders have been covered elsewhere in this book and will not be dealt with in this section which will concentrate on the first group where the neuropathy is the sole or primary part of the disease.

Charcot–Marie–Tooth disease and related disorders

CMT disease is a group of neuropathies that are clinically and genetically heterogeneous. They are also referred to as hereditary motor and sensory neuropathies (HMSN) although CMT is now the more commonly used term. CMT is characterized clinically by distal muscle wasting and weakness, reduced reflexes, impaired distal sensation and variable foot deformity, and neurophysiologically by a motor and sensory neuropathy. There is a wide variation in the age of onset and the severity of CMT, the variation depending to a large extent on the underlying genetic defect. Traditional clinical classifications differentiate between CMT (which has both motor and sensory involvement; Table 9.6), HSAN (more sensory and autonomic and less motor; Table 9.7) and dHMN (only motor; Table 9.8). Certain forms of CMT and HSAN are very difficult to distinguish clinically. Some recently described causative genes for axonal CMT also cause forms of dHMN. Therefore, the same phenotypes may be caused by different genes and the same gene may cause different phenotypes. Technology is not yet advanced enough to allow the rapid screening in an individual patient of all genes identified so far. Therefore, a classification system (Table 9.6) based on clinical features of neurophysiology and neuropathology as well as the genetic cause, when known, is the most useful current classification for the practising clinician.

An approach to the diagnosis of CMT and related disorders

1 *Is the neuropathy hereditary?* Where a patient attends with an obviously affected family member or there is a positive family history, a genetic neuropathy is likely. Unfortunately, many patients are from small families (especially UK, USA and North European) and extensive family histories are not available. Furthermore, rates of non-paternity in Western societies are at least 10%. Factors that may help the clinician decide that the neuropathy in 'sporadic' patients is hereditary include:

(a) A long, slowly progressive history.

(b) The presence of foot deformity such as pes cavus in an adult patient (Figure 9.9).

(c) The absence of positive sensory symptoms in patients with clear sensory signs.

(d) In the demyelinating forms of CMT (CMT1), neurophysiology can be very useful in distinguishing hereditary from acquired neuropathies as the motor conduction velocities are usually uniformly slow in the common hereditary neuropathies.

2 *Classifying the neuropathy*. Is the neuropathy most compatible with CMT, hereditary neuropathy with liability to pressure palsies (HNPP), HSAN or dHMN?

(a) CMT is numerically the most likely diagnosis.

(b) CMT is a motor *and* sensory neuropathy although the patients may not have sensory symptoms and sometimes no sensory signs (the most sensitive sensory sign is a reduction in distal vibration sensation).

(c) Because dHMN (Table 9.8) can be indistinguishable clinically from CMT it is often necessary to perform a neurophysiological examination to differentiate between these two conditions. The sensory action potentials (SAPs) should always be involved (reduced or absent) in CMT and normal in dHMN.

Table 9.6 Classification of Charcot–Marie–Tooth (CMT) disease.

Type	Gene/locus	Specific phenotype
Autosomal dominant CMT1 (AD CMT1)		
CMT1A	Dup 17p (PMP22)	Classic CMT1
	PMP22 (point mutation)	Classic CMT1/DSD/CHN
CMT1B	MPZ	CMT1/ DSD/CHN/CMT2
CMT1C	LITAF	Classic CMT1
CMT1D	EGR2	Classic CMT1/DSD/CHN
CMT1	NEFL	CMT2 but can have slow MCVs in CMT1 range +/– early onset severe disease
Hereditary neuropathy with liability to pressure palsies (HNPP)		
HNPP	Del 17p (PMP-22)	Typical HNPP
	PMP-22 (point mutation)	Typical HNPP

Table 9.6 *Continued*

Type	Gene/locus	Specific phenotype
X-linked CMT1 (CMT 1X)		
CMT1X	GJB1	Males CMT1 (+/– patchy MCVs)/females CMT2
Autosomal recessive CMT1 (AR CMT1)		
CMT4A	GDAP1	CMT1 or CMT2 usually early onset and severe / vocal cord and diaphragm paralysis described / rare AD CMT2 families described
CMT4B1	MTMR2	Severe CMT1/facial/bulbar/focally folded myelin
CMT4B2	MTMR13	Severe CMT1/glaucoma/focally folded myelin
CMT4C	KIAA1985	Severe CMT1/scoliosis/cytoplasmic expansions
CMT4D (HMSNL)	NDRG1	Severe CMT1/gypsy/deafness/tongue atrophy
CMT4E	EGR2	CMT1/DSD/CHN phenotype
CMT4F	Periaxin	CMT1/more sensory/focally folded myelin
CCFDN	CTDP1	CMT1/gypsy/cataracts/dysmorphic features
HMSN Russe	10q22–q23	CMT1
AR CMT1	PMP22 (point mutation)	Classic CMT1/DSD/CHN
AR CMT1	MPZ	CMT1/DSD/CHN/CMT2
Autosomal dominant CMT2 (AD CMT 2)		
CMT2A	KIF1Bβ	Classic CMT2
CMT2A	MFN2	Classic CMT2/more progressive/optic atrophy
CMT2B	RAB7	CMT2 with predominant sensory involvement and sensory complications
CMT2C	12q23–q24	CMT2 with vocal cord and respiratory involvement
CMT2D	GARS	CMT2 with predominant hand wasting/weakness or dHMN-V
CMT2E	NEFL	CMT2 but can have slow MCVs in CMT1 range +/– early onset severe disease
CMT2F	HSP27	Classic CMT2 or dHMN-II
CMT2G	12q12–q13.3	Classic CMT2
CMT2L	HSP22	Classic CMT2 or dHMN-II
CMT2	MPZ	CMT1 or CMT2
CMT2 (HMSNP)	3q13.1	CMT2 with proximal involvement
Autosomal recessive CMT2 (AR CMT2)		
ARCMT2A	LMNA	CMT2 proximal involvement and rapid progression described/also causes muscular dystrophy/cardiomyopathy/lipodystrophy
ARCMT2B	LINKAGE	Typical CMT2
ARCMT2	GDAP1	CMT1 or CMT2 usually early onset and severe/vocal cord and diaphragm paralysis described/rare AD CMT2 families described
X-linked CMT2		
CMT 2X	Xq24–q26	CMT2 with deafness/mental retardation
Dominant intermediate CMT (DI-CMT)		
DI-CMTA	10q24.1–25.1	Typical CMT
DI-CMTB	DNM2	Typical CMT
DI-CMTC	YARS	Typical CMT
Hereditary neuralgic amytrophy		
HNA	SEPT9	Recurrent neuralgic amyotrophy

AD, autosomal dominant; AR, autosomal recessive; CCFDN, congenital cataract with facial dysmorphism and neuropathy; CTDP1, CTD phosphatase 1; Cx32, connexin 32; Del, deletion; DMN2, dynamin 2; Dup, duplication; EGR2, early growth response 2; GARS, glycyl-tRNA synthetase; GDAP1, ganglioside-induced differentiation-associated protein 1; HSP 22, heat shock 22 kDa protein 8; HSP 27, heat shock 27 kDa protein 1; LITAF, lipopolysaccharide-induced tumour necrosis factor; LMNA, Lamin A/C; KIAA1985, KIAA1985 protein; KIF1Bβ, Kinesin family member 1B-β; MFN2, Mitofusin 2; MPZ, myelin protein zero; MTMR2, myotubularin-related protein 2; MTMR13, myotubularin-related protein 13; NDRG1, N-myc downstream-regulated gene 1; NEFL, neurofilament, light polypeptide 68 kDa; PMP-22, peripheral myelin protein 22; PRX, periaxin; SEPT9, septin 9; RAB7, RAS-associated protein RAB7; YARS, tyrosyl-tRNA synthetase.

Table 9.7 Classification of the hereditary sensory and autonomic neuropathies (HSAN).

Type	Inheritance	Gene/locus	Specific phenotype
HSAN I	AD	SPTLC1	Mainly sensory, sensory complications Occasionally motor early, males more severe
CMT2B	AD	RAB7	Sensorimotor, sensory complications, no pain
HSAN 1	AD	3p24–p22	Sensory, cough, gastroesophageal reflux
HSAN II	AR	HSN2	Severe sensory complications, mutilations Onset first two decades
HSAN III	AR	IKBKAP	Familial dysautonomia or Riley–Day syndrome Prominent autonomic, absence fungiform papillae of the tongue
HSAN IV	AR	NTRK1	Congenital insensitivity to pain with anhydrosis (CIPA) with severe sensory involvement, anhydrosis, mental retardation Unmyelinated fibres mainly affected
HSAN V	AR	NTRK1	Congenital insensitivity to pain with mild anhydrosis No mental retardation Small myelinated fibres mainly affected
HSAN V	AR	NGFB	Congenital insensitivity to pain, minimal autonomic No mental retardation Mainly unmyelinated fibres affected
Channelopathy associated insensitivity to pain	AR	SCN9A	Congenital insensitivity to pain

AD, autosomal dominant; AR, autosomal recessive; HSN2, HSN2 gene; IKBKAP, IκB kinase complex-associated protein; NGFB, nerve growth factor beta gene; NTRK1, tyrosine kinase A receptor; SCN9A, sodium channel 9A; SPLTC1, serine palmitoyltransferase, long chain base subunit-1.

Table 9.8 Classification of the distal hereditary motor neuropathies (dHMN).

Type	Inheritance	Gene/locus	Specific phenotype
HMN I	AD	Unknown	Juvenile onset dHMN
HMN II	AD	HSP27	Adult onset typical dHMN/CMT2F
HMN II	AD	HSP22	Adult onset typical dHMN/CMT2L
HMN III	AR	11q13	Early onset, slowly progressive
HMN IV	AR	11q13	Juvenile onset, diaphragmatic involvement
HMN V	AD	GARS	Upper limb onset, slowly progressive/CMT2D
HMN V	AD	BSCL2	Upper limb onset, +/– spasticity lower limbs
HMN VI	AR	IGHMB2	Spinal muscle atrophy with respiratory distress (SMARD1), infantile onset respiratory distress
HMN VII	AD	2q14	Adult onset, vocal cord paralysis
HMN VII	AD	DCTN1	Adult onset, vocal cord paralysis/facial weakness
HMN/ALS4	AD	SETX	Early onset, pyramidal signs
HMN-J	AR	9p21.1–p12	Juvenile onset, pyramidal features, Jerash

BSCL2, Berardinelli–Seip congenital lipodystrophy gene; DCTN1, dynactin1; GARS, glycyl-tRNA synthetase; HSP 22, heat shock 22 kDa protein 8; HSP 27, heat shock 27 kDa protein 1; IGHMB2, immunoglobulin μ binding protein 2; SETX, sentaxin.

(d) The neuropathy of HNPP is usually easily distinguished from CMT as the patient normally has a history of recurrent pressure palsies but later accumulates neurological deficits. The neurophysiological findings are usually patchier in HNPP than in the common forms of CMT1.

(e) Most forms of HSAN (Table 9.7) have more sensory and autonomic involvement and less motor involvement than CMT. The presence of neuropathic pain makes HSAN1 more likely and is a useful differentiating feature.

Charcot–Marie–Tooth disease

CMT disease is the most common of the hereditary neuropathies. The classification of CMT is in a state of constant flux reflecting the rapid advances in the identification of the underlying

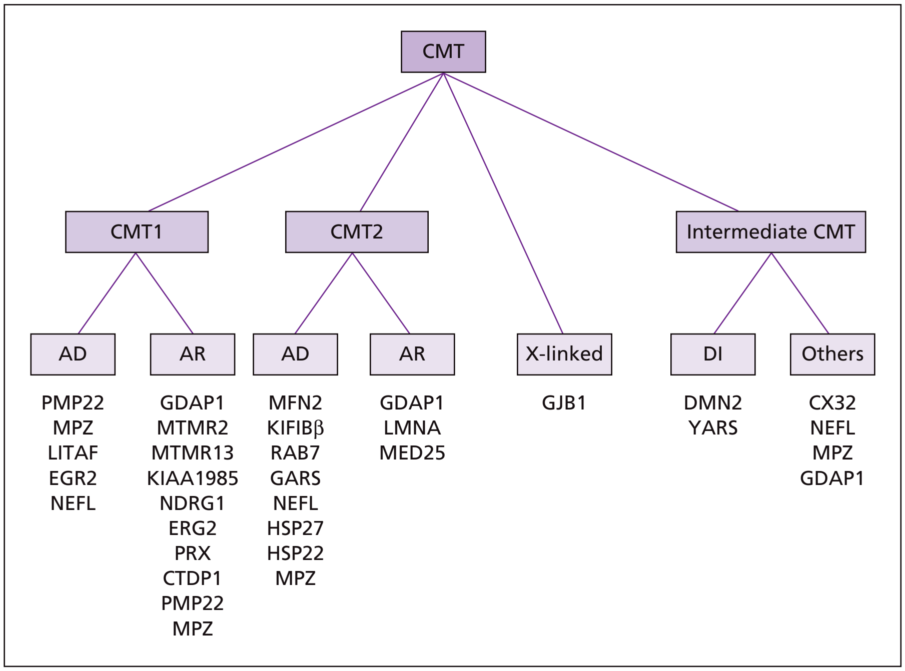

Figure 9.11 Current known causative genes for Charcot–Marie–Tooth (CMT) disease. AD, autosomal dominant; AR, autosomal recessive; CTDP1, CTD phosphatase, subunit 1; DI, dominant intermediate; DMN2, dynamin 2; EGR2, early growth response 2; GARS, glycyl-tRNA synthetase; GDAP1, ganglioside-induced differentiation-associated protein 1; GJB1, gap junction protein, beta 1; HSP 22, heat shock protein 22 kDa protein 1; HSP 27, heat shock protein 27 kDa protein 8; KIAA1985, KIAA1985 protein; KIF1Bβ, kinesin family member 1B-β; LITAF, lipopolysaccharide-induced tumour necrosis factor; LMNA, lamin A/C; MED25, mediator of RNA polymerase II, subunit 25; MFN2, mitofusin 2; MPZ, myelin protein zero; MTMR2, myotubularin-related protein 2; MTMR13, myotubularin-related protein 13; NDRG1, N-*myc* downstream-regulated gene 1; NEFL, neurofilament, light polypeptide 68 kDa; PRX, periaxin; PMP-22, peripheral myelin protein 22; RAB7, RAS-associated protein RAB7; YARS, tyrosyl-tRNA synthetase.

causative genes (Figure 9.11). Despite the rapid genetic advances the most useful method of classification for clinicians is a combination of clinical presentation, neurophysiology and inheritance pattern.

CMT is classified as either demyelinating (CMT1) if the median (or ulnar) nerve motor conduction velocity (MCV) is <38 m/s or axonal (CMT2) if the median MCV is >38 m/s (Table 9.5). The concept of an intermediate form of CMT with median MCVs in the intermediate range (25–45 m/s) has been around since the 1970s and although sometimes out of favour it can be helpful in directing genetic diagnosis.

The inheritance pattern may not be clinically obvious until a genetic diagnosis has been established as de novo autosomal dominant (AD) mutations, autosomal recessive (AR) mutations and other factors may obscure it. In most UK, north European and US populations where there are few consanguineous marriages, about 90% of cases of CMT are either AD or X-linked; the social background of the population should always be taken into account.

Autosomal dominant CMT1

Classic CMT1

The most common form of CMT in most populations is AD CMT1 and most patients present with a 'classic CMT' phenotype in the first two decades with motor symptoms in the lower limbs, e.g. difficulty walking or foot deformity. On examination, they have evidence of distal wasting and weakness and hyporeflexia affecting the lower limbs to a greater extent than the upper limbs. Distal sensory loss and foot deformity are frequent findings. Neurophysiologically, the median MCVs are <38 m/s and the SAPs are either reduced or absent. Nerve biopsies are no longer necessary to make the diagnosis but if performed show a demyelinating neuropathy with classic onion bulbs (Plate 9.1).

If there is a clear family history of AD inheritance, or if the patient is apparently 'sporadic', then the most likely diagnosis is CMT1A secondary to duplication of the peripheral myelin protein 22 gene (*PMP22*). In a European population this duplication accounts for 70% of all CMT1 cases. Mutations in the *PMP22* gene can also cause CMT1A but a wider spectrum of phenotypes is described.

CMT1B is less common and is caused by mutations in the myelin protein zero gene (*MPZ*). Patients may present with the classic CMT1 phenotype but are more likely to present with either a more severe, early onset form of CMT1 or a much milder, late onset form of CMT with median MCVs in the axonal range. As a result *MPZ*-related CMT can be classified as intermediate CMT.

Mutations in *EGR2* and *LITAF* are very rare and account for less than 1% of cases each and have no particular distinguishing features. Mutations in *NEFL* (neurofilament light polypeptide) were originally described as a cause of CMT2. Some patients with *NEFL* mutations have median MCVs in the demyelinating range and so *NEFL*-related CMT could be classified as intermediate CMT.

Severe CMT1 (HMSN III, Dejerine–Sottas disease, congenital hypomyelinating neuropathy)

The severe cases of CMT1 used to be called HMSN III in older classifications and were subdivided into Dejerine–Sottas disease (DSD) and congenital hypomyelinating neuropathy (CHN) depending on the underlying pathology. They usually present in the first decade with very slow MCVs and a more severe neuropathy than classic CMT1. It was thought that most of these cases were recessive but we now know they are usually secondary to de novo dominant mutations in the three genes that commonly cause CMT1 (*PMP22*, *MPZ*, *EGR2*). Mutations in these three genes, which cause the DSD/CHN phenotype, can also occasionally be inherited in an autosomal recessive fashion (Table 9.6).

Hereditary neuropathy with liability to pressure palsies

HNPP is an autosomal dominant condition usually caused by a deletion of the same portion of chromosome 17 duplicated in CMT1A. Point mutations in *PMP22* can also rarely cause HNPP. Most patients with HNPP present with episodic recurrent pressure palsies, although atypical presentations have been described. Diagnostically, an important point is that although patients may present with only one nerve clinically involved at a particular time, there is always a more generalized patchy demyelinating neuropathy neurophysiologically. Screening for the chromosome 17 deletion is therefore not warranted in isolated pressure palsies that do not have electrophysiological abnormalities outside the clinically involved nerve.

X-linked CMT1

The X-linked form of CMT1 is caused by mutations in the gap junction β1 gene (*GJB1*) which codes for connexin 32 (Cx32). This is the second most common form of CMT. Over 300 mutations have been described in *GJB1*. Males are more severely affected than females. The MCVs in affected males are usually in the demyelinating range. Conversely, the MCVs in the females are usually in the axonal range but can be in the demyelinating range. Connexin 32 related CMT is therefore another form of intermediate CMT.

Patients (especially males) can have a rather patchy neuropathy both clinically and neurophysiologically with less uniform conduction slowing, differences in conduction velocities between nerves (e.g. ulnar and median) and more pronounced dispersion than that seen with AD CMT1. This can lead to difficulties in diagnosis in patients without a family history and occasionally to patients being diagnosed with CIDP leading to unnecessary immunosuppressive therapy. CNS involvement is occasionally seen and is usually mild (extensor plantars, mild deafness, abnormal brainstem evoked potentials).

Autosomal recessive CMT1

In communities where consanguinity is high AR CMT may account for 30–50% of all CMT cases. There are now 10 genes described that can cause AR CMT1 (including the three genes *PMP22*, *MPZ* and *EGR2* that more commonly cause AD or de novo dominant CMT1). Unfortunately, there is no one gene that is a major cause of AR CMT1 which makes the diagnosis difficult for the clinician presented with a patient with presumed AR CMT1. Further confusion arises as AR CMT1 is called CMT4 in the genetic literature and hence the various forms of AR CMT1 are also classified as CMT4A, CMT4B, and so on.

Although no one algorithm is suitable for the diagnosis of AR CMT1, there are some simple clinical rules that can be used to aid diagnosis:

1 As a general rule, AR forms of CMT have an earlier onset and are more severe than AD cases. They usually start as a length dependent neuropathy but are more likely to progress to involve the proximal muscles and to result in loss of ambulation than AD patients. Associated clinical features, the ethnic background of patients and specific neuropathological features can aid the diagnosis (Table 9.6).

2 Neurophysiology may be difficult, as in severe cases all the nerves may be unexcitable. In these cases nerve biopsies can be particularly useful. Biopsy is also useful in AR CMT1 in general as specific features in nerve biopsies may make a particular genetic diagnosis more likely. This is the major diagnostic use for nerve biopsy in genetic neuropathies.

3 Specific phenotypes in AR CMT1 (CMT4) are recognized:

(a) CMT4A secondary to mutations in *GDAP1* is usually an early onset progressive neuropathy and can be associated with diaphragmatic and vocal cord involvement. Mutations in *GDAP1* can also cause AR CMT2 making *GDAP1*-related CMT another intermediate form of CMT.

(b) Nerve biopsies showing focally folded myelin are characteristic of CMT4B1 (*MTMR2* mutations) and CMT4B2 (*MTMR13* mutations) although this finding has also been described with *MPZ* mutations and in CMT4F secondary to periaxin mutations.

(c) Severe and early scoliosis is seen with CMT4C because of mutations in the *KIAA1985* gene. Patients with mutations in this gene also have characteristic nerve biopsy features including basal membrane onion bulbs and multiple cytoplasmic processes of the Schwann cells of unmyelinated axons.

(d) Three forms of AR CMT1 are largely confined to patients of Balkan Romany origin. CMT4D secondary to *NDRG1* mutations is characterized by a demyelinating neuropathy with a high incidence of deafness. Tongue atrophy has also been described in this form of CMT. Another form of AR CMT1 seen in this Romany population is CCFDN (congenital cataract, facial dysmorphism and neuropathy syndrome) secondary to *CTDP1* mutations. The gene for the third form of CMT in this population, HMSN Russe, has not been identified yet.

(e) A phenotype ranging from a severe DSD type phenotype to a milder neuropathy with mainly sensory involvement is seen in CMT4F secondary to periaxin mutations.

To summarize, although there are many different genes identified as causing AR CMT1 careful phenotyping of the patients together with consideration of the ethnic background can help guide the genetic diagnosis.

Autosomal dominant CMT2

The true prevalence of CMT2 is not known. However, any adult presenting with a long-standing mild axonal neuropathy without an obvious family history and where an acquired cause has not been identified may have a CMT2 but this is difficult to prove. Eight causative genes for AD CMT2 have been described (Table 9.6). These still account for only about 25% of the total cases of AD CMT2 and until all the causative genes for CMT2 are identified, we will not know the true prevalence of this condition.

Autosomal dominant CMT2 can be divided into three different groups by phenotype which can be used to direct genetic testing.

1 Most patients with AD CMT2 present with the 'classic CMT' phenotype, indistinguishable from AD CMT1. The neurophysiology revealing an axonal sensorimotor neuropathy distinguishes between the two. Nerve biopsies are rarely performed in patients with AD CMT2 as a non-diagnostic axonal neuropathy is usually described. The major cause of the classic phenotype are mutations in mitofusin 2 (*MFN2*) causing CMT2A. Mutations in this gene account for approximately 20% of all cases of AD CMT2 in all populations tested so far. Furthermore, approximately 20% of the mutations are de novo, explaining why so many of these patients have normal parents. Patients with mutations in *MFN2* can also present early and with a more severe phenotype with fairly rapid progression to proximal muscle involvement and loss of ambulation. Occasionally, patients may have brisk reflexes. Mutations in *MFN2* also cause axonal CMT with optic atrophy (HMSN VI in previous classifications). In patients with classic AD CMT2 and no mutation in *MFN2* both *MPZ* and *NEFL* should be screened as they can cause this phenotype. Two recently described heat shock protein genes (*HSP27* and *HSP22*) may also rarely cause the classic CMT2 phenotype. These two genes are of additional interest as they can also cause a purely motor phenotype, dHMN type II (Table 9.8; i.e. same gene, different phenotype).

2 The second phenotype seen with AD CMT2 has much more sensory involvement than is usually seen with CMT. These patients have been described as having an 'autosomal dominant inherited neuropathy with prominent sensory loss and ulceromutilating features'. They were originally classified as CMT2B. Presentation is in the second or third decade with typical motor CMT features but also severe sensory complications including ulcerations, osteomyelitis and amputations. The causative gene for CMT2B is *RAB7*. The presentation of these patients is also very similar to patients with HSAN1 secondary to mutations in the *SPTLC1* gene (Table 9.7; i.e. different genes, same phenotype). Patients with *SPTLC1* mutations usually have less motor involvement at presentation and also lancinating pain, an unusual feature in hereditary neuropathies. Sometimes conduction velocities can be in the demyelinating range and males are often severely affected. There remain other families with this phenotype who do not have mutations in either *SPTLC1* or *RAB7*, suggesting other unidentified genes can also cause this phenotype.

3 The third phenotype seen with AD CMT2 is upper limb predominant CMT2, classified as CMT2D. Patients were originally described presenting with wasting and weakness of the small muscles of the hand (onset can also be unilateral and misdiagnosed as thoracic outlet syndrome) with much later involvement of the distal lower limb muscles. Interestingly, as with mutations in *HSP27* and *HSP22*, some of these patients had no sensory involvement and were classified as dHMN type V (Table 9.8). CMT2D and dHMN V have now been shown to be allelic. The causative gene is *GARS*. Some patients with the dHMN V phenotype (no sensory involvement) have also been described to have mutations in the *BSCL2* gene which usually causes Silver syndrome (spastic legs and distal amyotrophy of the upper limbs) but can present in 33% of cases with just amyotrophy of the upper limbs. Other families have been described with this phenotype that do not have mutations in either *GARS* or *BSCL2*.

Autosomal recessive CMT2

There are only two causative genes for AR CMT2 (Table 9.6). Mutations in lamin A/C (*LMNA*) cause AR CMT2A. Moroccan and Algerian families were reported with this phenotype. Most patients present in the second decade with a severe CMT phenotype including proximal muscle involvement although some patients have been reported with a milder phenotype. Lamin A/C mutations have been associated with a wide spectrum of phenotypes including Emery–Dreyfuss muscular dystrophy, cardiomyopathy, Dunniugan-type familial partial lipodystrophy and many others.

The second form of AR CMT2, AR CMT2B, has only been described in one Costa Rican family and the gene for this has yet to be identified. The phenotype of AR CMT2B is milder than seen with the other AR CMT2 genes and is more like classic CMT2.

Mutations in *GDAP1* have been described above as a cause of AR CMT1 (CMT4A) but they can also cause AR CMT2 with a similar severe early onset phenotype which can include vocal cord paresis.

X-linked CMT2

One X-linked form of CMT2 has been described linked to Xq24-Q26, but no gene has been identified for this.

Dominant intermediate CMT

It is increasingly recognized that many forms of CMT can present with MCVs in the intermediate range as discussed above. These include patients with X-linked CMT resulting from *GJB1* mutations, patients with AD CMT caused by *MPZ* or *NEFL* mutations and patients with AR CMT caused by *GDAP1* mutations. In addition to these forms of intermediate CMT, two genes have recently been described (*DNM2* and *YARS*) that cause classic CMT with intermediate MCVs and these have been classified as dominant intermediate CMT (Table 9.6).

Hereditary sensory and autonomic neuropathy

HSAN are much rarer than CMT but many of the genes for these disorders have been identified (Table 9.7).

Generally, these disorders are characterized by prominent sensory and autonomic involvement and less motor involvement than CMT. The sensory involvement can be severe and result in mutilating injuries. Education of the patients to try to prevent these complications is crucial.

HSAN1 secondary to *SPTLC1* mutations has already been described above. This disease is more appropriately termed HSN as there is usually no autonomic involvement. All other forms of HSAN are rare. HSAN II is an early onset, autosomal recessive, severe sensory neuropathy with prominent sensory complications and is caused by mutations in the *HSN2* gene.

Riley–Day syndrome is a distinct autosomal recessive neuropathy seen in Ashkenazi Jews and characterized by mainly autonomic involvement but it also involves the PNS, particularly the sensory nerves. The causative gene is the *IKBKAP* gene. Presentation is often in infancy or childhood with poor feeding, swallowing difficulties and recurrent chest infections.

HSAN IV and V are both AR neuropathies characterized by congenital insensitivity to pain. HSAN IV (also called congenital insensitivity to pain with anhydrosis [CIPA]) presents with a severe sensory neuropathy, anhydrosis and mental retardation and is caused by mutations in the *NTRK1* gene, a receptor for nerve growth factor. HSAN V is similar but without the mental retardation or significant anhydrosis. This phenotype has been described with both *NTRK1* mutations and also with *NGFB* mutations. A recent development in the hereditary sensory neuropathies has been the identification of homozygous mutations in the gene (*SCN9A*) for the voltage-gated sodium 1.7 channel ($NA_v1.7$) in a form of HSAN resembling type V and termed channelopathy-associated insensitivity to pain.

Distal hereditary motor neuropathies

The dHMNs are a complex group of disorders (Table 9.8) also referred to as distal spinal muscular atrophies (distal SMA). Forms that resemble CMT are discussed above.

Distal HMN II is the classic form of AD dHMN and is caused by mutations in the *HSP27* and *HSP22* genes. These patients present with classic CMT but without any sensory involvement. Distal HMN I (no gene identified) is a similar AD disorder but with earlier onset. There are many other forms but the genes are only known for a few of these. Mutations in *GARS* and *BSCL2* cause dHMN V as described above.

Distal HMN VI is an unusually severe AR form of dHMN that presents in infancy with respiratory and distal limb involvement (called spinal muscle atrophy with respiratory distress type 1 [SMARD1]) and is caused by mutations in the *IGHMBP2* gene.

Mutations in dynactin (*DCTN1*) cause one of two forms of dHMN type VII, which is characterized by vocal cord paralysis and progressive weakness and atrophy of the face, hands and legs. Another very similar form, also called dHMN VII with vocal cord paralysis has been mapped to a different locus.

Finally, missense mutations in sentaxin (*SETX*) can cause a form of dHMN with pyramidal features. Nonsense mutations in the same gene cause autosomal recessive ataxia oculomotor apraxia type 2 (AOA2).

As can be seen in Table 9.8, there are other forms of dHMN described for which no causative genes have yet been identified.

Hereditary neuralgic amyotrophy

HNA is an autosomal dominant condition caused by mutations in the Septin 9 gene and characterized by recurrent episodes of typical brachial neuritis. The attacks are characterized by pain, weakness and sensory disturbance in the brachial plexus distribution. These attacks are indistinguishable from sporadic brachial neuritis but are recurrent, often starting in childhood.

Importance of a genetic diagnosis in CMT and related disorders

A major issue throughout the world is the lack of availability of testing for the rarer genes causing CMT and related disorders. Many countries offer routine diagnostic testing for the common CMT1 (chromosome 17 duplication, *PMP22*, *MPZ*, *Cx32*) and CMT2 (*MFN2*) genes. Most of the other genes are only available through research laboratories.

An accurate genetic diagnosis is extremely important for these patients. There are obvious benefits including diagnostic testing for other family members, accurate genetic counselling and prognosis, predictive and antenatal testing but an accurate diagnosis also prevents patients from having invasive diagnostic tests, e.g. nerve biopsies and lumbar punctures. In certain situations where inflammatory neuropathies are being considered a genetic diagnosis can prevent a trial of potentially dangerous immunosuppressive therapy.

The era of treatment for genetic neuropathies is here. The first therapeutic trials in CMT have just begun (ascorbic acid for CMT1A) and it seems likely that any treatments developed (at least at the trial stage) will be gene specific, making the case for an accurate genetic diagnosis even more convincing.

Familial amyloid polyneuropathy

FAP is an autosomal dominant condition first described in Portugal in 1952. The amyloidoses are characterized by deposition of a fibrillar β-pleated protein in the extracellular space of many organs. Only AL (light chain) amyloidosis and FAP cause a generalized neuropathy with autonomic involvement. AL amyloid is discussed below. Within the familial amyloidoses there are three different forms of FAP classified by the constituent amyloid-forming protein: transthyretin (TTR), apolipoprotein A-1 (Apo A-1) and gelsolin.

Transthyretin-related familial amyloid polyneuropathy

Clinical features

The cardinal clinical features of TTR-related FAP are of a sensory motor peripheral neuropathy usually with autonomic involvement, a cardiomyopathy and to a lesser extent vitreous involvement. Other systems can be involved. Over 80 mutations in TTR have been described, the most common of which is the index Met30 point mutation. Clinical features do not always correlate well with a specific mutation.

Patients with TTR Met30 usually present with painful dysaesthesia in the lower limbs progressing to a severe mixed polyneuropathy. Early there is greater small fibre susceptibility giving rise to lack of pain and temperature sensation, but eventually all sensory modalities are involved. Mutilating injuries can occur. Later motor involvement is universal, with upper limb involvement occurring months to years after lower limb manifestations. Carpal tunnel syndrome as a presenting feature is rare in TTR Met30. Autonomic involvement occurs frequently and can be severe and early.

Neurophysiological studies confirm an axonal neuropathy although SAPs may be normal early in the course of the disease, reflecting the mainly small fibre involvement. Cardiac involvement is common, presenting as an arrhythmia, heart block or heart failure, and amyloid deposition results in abnormal echocardiographic appearances. Vitreous involvement is more common in Swedish than Portuguese TTR Met30 patients and may be the presenting feature. Kidneys and, more rarely, pulmonary or bone involvement also occur.

Other common mutations include TTR Tyr 77 and TTR Ala 60. FAP TTR Tyr 77 has a high incidence of carpal tunnel syndrome but absent vitreous involvement. FAP TTR Ala 60 is mainly seen in patients of Irish descent and typically presents in the sixth decade with more prominent small and large fibre sensory loss than TTR Met30. Cardiomyopathy is a major and commonly a presenting feature.

CNS involvement in FAP TTR is very rare and, although postmortem studies have shown leptomeningeal amyloid deposition, this is usually asymptomatic. Oculoleptomeningeal amyloidosis (OLMA) is associated with TTR point mutations. The clinical features vary even within a kindred and include vitreous opacities, progressive dementia, stroke, subarachnoid haemorrhage, ataxia, hydrocephalus, seizures, spasticity and episodes of fluctuating consciousness often with focal neurological signs. The hallmarks of the CNS disease are meningeal enhancement of the brain and spinal cord on MRI and a raised CSF protein.

Pathology

The pathological changes in the PNS are similar in FAP and AL amyloidosis. The amyloid in the PNS appears as extracellular, amorphous, eosinophilic deposits, which are found both diffusely in the endoneurium and epineurium and surrounding endoneurial and epineurial blood vessels. They are also present in sensory and autonomic ganglia. In milder cases there is predominant loss of small myelinated and unmyelinated axons; at later stages larger myelinated fibres are also lost. The pathology is predominantly one of axonal degeneration with some regenerative activity. Segmental demyelination has also been described. Congo red staining has apple green birefringence under polarized light and under electron microscopy (EM) rigid 10–15 nm fibrils are seen (Plate 9.2).

Diagnosis

The most important step in the diagnosis of TTR-related FAP is having a clinical suspicion. It should always be considered in patients with a family history and a neuropathy and/or cardiomyopathy, carpal tunnel syndrome or vitreous deposits. The diagnosis should also be considered in patients with an unexplained small fiber neuropathy especially with autonomic involvement or a cardiomyopathy regardless of family history. Neurophysiologically, the neuropathy is an axonopathy and has no specific features.

The diagnosis of amyloid can be made by direct examination of biopsy material from rectum, peripheral nerve, heart, subcutaneous fat or other tissue depending on the presentation. Congo red staining with apple green birefringence under polarized light is the primary examination. Immunohistochemistry with monoclonal antibodies against TTR or the λ or κ light chains differentiates TTR amyloid from light chain amyloid but the method is neither 100% sensitive nor specific. Light chains should be sought by immunofixation in urine and serum if AL amyloid is suspected and the antibodies to TTR are negative.

Sequencing of the TTR gene is widely available for genetic testing and confirmation of a histopathological diagnosis. Predictive testing remains difficult because of uncertainties about the penetrance of certain mutations.

Once the diagnosis is made the extent and stage of the disease must be assessed by iodine-123 labelled serum amyloid protein scan, especially if liver transplantation (see below) is being considered.

Treatment

Ninety per cent of TTR is produced in the liver. Until the early 1990s the treatment of TTR-related FAP was limited to symptomatic treatments and rehabilitative measures. Since then liver transplantation has been used in the treatment of TTR-related FAP. More than 700 liver transplants have been performed for TTR-related FAP worldwide. The consensus is that liver transplantation halts or slows the progression of TTR-related FAP in most Met30 patients. The 1-year survival has improved from 70% to 90% and a preliminary 10-year survival of 73% following transplant has been reported. There is concern that patients with mutations other than Met30 do not do as well.

Although liver transplantation is the first treatment for TTR amyloidosis and should be considered in affected patients, it is associated with a significant mortality and other safer and more effective treatments are being researched but none is in routine use to date.

Prognosis

The average life expectancy for patients with untreated TTR-related FAP is about 10 years but varies with ethnicity, mutation and treatment. This figure is likely to improve further as the optimum conditions and timing for liver transplantation are determined and as newer genetic and chemotherapeutic treatments are developed.

Apolipoprotein A-1 related FAP

One type of FAP, originally described in an Iowa kindred, has been shown to be associated with deposition of a variant apolipoprotein A-1. The phenotype is similar to that of FAP TTR Met30 except for a higher incidence of renal amyloidosis and severe gastric ulcer disease.

Gelsolin-related FAP

Gelsolin amyloidosis was first described in a Finnish kindred. This usually presents in the thirties with corneal lattice dystrophy caused by amyloid deposition in the corneal branches of the trigeminal nerve. This is followed by a progressive cranial neuropathy. The facial nerve is the most common cranial nerve involved with the upper fibres as manifested by forehead muscle weakness initially being affected. Other cranial nerves may also be affected including the vestibulocochlear, hypoglossal and trigeminal with varying clinical manifestations. Peripheral nerve and autonomic involvement is usually mild.

The fibril protein in this type of amyloidosis is an abnormal fragment of a plasma protein, gelsolin, a calcium-binding protein that fragments actin filaments.

Acquired neuropathies

The acquired peripheral nerve diseases are a diverse group of conditions with a variety of pathogenic mechanisms. Some are primary peripheral nerve disorders affecting a single system. Many are disorders with multi-system dysfunction such as the neuropathies associated with diabetes, autoimmune diseases or toxic exposures. The inflammatory neuropathies, in their various guises, constitute the largest group of peripheral nerve disorders.

Inflammatory neuropathies

The inflammatory neuropathies (Table 9.9) are a diverse group of peripheral nerve disorders linked by their presumed immune-mediated pathogenesis. They are characterized pathologically by inflammatory infiltration of the peripheral nerves associated with destruction of myelin and/or axons. The inflammatory neuropathies are typified by the idiopathic demyelinating neuropathies, both chronic and acute, and the closely related neuropathies associated with paraproteinaemia. However, vasculitic, infectious and parainfectious, paraneoplastic and more recently diabetic plexopathy, amongst others, are included. Some of these may be thought of as primary disorders of the PNS (e.g. GBS and CIDP) and others secondary to a systemic immune process with subsequent

Table 9.9 Inflammatory neuropathies.

ACUTE

Guillain-Barré (GBS) variants

- Acute inflammatory demyelinating polyradiculoneuropathy
- Acute motor axonal neuropathy
- Acute motor sensory axonalneuropathy
- Fisher syndrome and other regional variants
  - Pharyngeal-cervical-brachial
  - Paraparetic
  - Facial palsies
  - Pure oculomotor
- Functional variants of GBS
  - Pure dysautonomia
  - Pure sensory GBS
  - Ataxic GBS

INTERMEDIATE

Subacute inflammatory demyelinating polyradiculoneuropathy

Vasculitic neuropathies (may present acutely, subacutely or chronically)

- Primary vasculitis
  - Polyarteritis nodosa
  - Churg–Strauss syndrome
  - Microscopic polyangiitis
  - Wegener's vasculitis
  - Non-systemic vasculitic neuropathy
  - Giant cell arteritis
- Systemic autoimmune diseases with associated vasculitis
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Sjögren's syndrome
  - Mixed connective tissue disease
- Other vasculitis
  - Diabetic and non-diabetic lumbosacral plexopathy

Other inflammatory neuropathies

- Serum sickness
- Infections (hepatitis B and C, HIV, Lyme disease), leprosy
- Malignancy (small cell lung cancer, lymphoma, leukaemia, renal and adenocarcinomas)
- Chemotherapy
- Paraneoplastic
  - Subacute sensory neuropathy/neuronopathy – small cell lung carcinoma and anti-Hu Abs
  - Other paraneoplastic tumour–antibody syndromes

CHRONIC

- Chronic inflammatory demyelinating polyradiculoneuropathy
- Multifocal motor neuropathy with conduction block
- Multifocal acquired demyelinating sensory and motor neuropathy
- Chronic relapsing axonal neuropathy
- Chronic ataxic sensory neuronopathy

CHRONIC, WITH PARAPROTEINAEMIAS

- Monoclonal gammopathy of undetermined significance
- Multiple myeloma
- Solitary plasmacytoma
- Lymphoma or chronic lymphocytic leukaemia
- Waldenström's macroglobulinaemia
- POEMS syndrome
- Cryoglobulinaemia
- Cold agglutinin disease

involvement of the peripheral nerves (e.g. the neuropathy associated with vasculitis and the connective tissue diseases).

Acute neuromuscular weakness and the inflammatory neuropathies

Acute neuromuscular weakness may be caused by disease of muscle, neuromuscular junction, peripheral nerve, roots or the CNS. The distinction between these sites of pathology can largely be made on clinical grounds, with supportive investigations where necessary (Chapters 3 and 19).

A differential diagnosis of acute inflammatory neuropathies exists (Table 9.9). By far the most common of these is GBS. The acute infectious neuropathies (poliomyelitis, diphtheria, HIV, tick paralysis) are dealt with in Chapter 8 and paraneoplastic neuropathies in Chapter 20.

Guillain–Barré syndrome and its variants

GBS is the most common cause of acute neuromuscular weakness in the developed world following the near eradication of polio, but certainly occurs worldwide. The incidence is about 1–2/100,000 population. There is no sex difference. It affects all ages including children and infants but is more frequent in older age groups. In some populations a seasonal variation in the incidence is reported coinciding with the seasonal incidence of predisposing infections (Table 9.10). In the developed world GBS is synonymous with acute inflammatory demyelinating polyradiculoneuropathy (AIDP) but axonal variants (occurring in 3–5% of cases in the developed world) are far more common in China, Japan and Mexico (see below).

Symptoms and signs

The diagnosis of GBS remains a clinical one, supported by investigations which may be normal in the early stages of disease. Patients present with a progressive ascending sensorimotor paralysis with areflexia, affecting one or more limbs and reaching a nadir in less than 4 weeks. Patients who progress beyond this time or present with 'recurrent GBS' are reclassified into subacute or chronic inflammatory demyelinating neuropathies (SIDP/CIDP, see below). Pain, cranial nerve involvement and autonomic disturbances with arrhythmias and labile blood pressure are often features. Papilloedema may occur, which if unrecognized and untreated may lead to blindness. A clinical diagnosis of GBS should be questioned if there is persistent asymmetrical weakness, bladder or bowel involvement or a sensory level suggestive of spinal cord pathology. Furthermore, the presence of a known toxin, HIV, diphtheria or tick exposure or neoplasia broadens the differential. In the first few days the examination may be normal and reflexes retained. However, some patients may progress to tetraparesis and require ventilation in as little as 48 hours and vigilance for either scenario is important. Functional variants exist with acute pure autonomic failure, pure sensory neuropathy and pure ataxic neuropathy described. Recognized regional variants (Table 9.9) are associated with particular serum antiganglioside antibodies (see below).

Table 9.10 Infections predisposing to Guillain–Barré syndrome.

Campylobacter jejuni
Cytomegalovirus
Mycoplasma pneumoniae
Epstein–Barr virus
HIV
Haemophilus influenzae

Investigations

Cerebrospinal fluid. In GBS the CSF is acellular or should contain <10 cells/mm^3. Ten per cent of patients have cell counts of 10–50 cells/mm^3 but these do not persist for more than a few days. Cell counts >50 cells/mm^3 should stimulate a search for an alternative diagnosis. Note that intravenous immunoglobulin (IVIG) can stimulate an aseptic meningitis and may provoke increased cell counts (as well as falsely raised CSF protein levels). CSF protein is usually raised for 4–6 weeks but may be normal in the first 7 days of illness and may also remain normal in a greater proportion of the regional variants (e.g. Fisher syndrome) than typical GBS. CSF pressure is typically normal but raised levels of CSF pressure and protein contribute to papilloedema.

Nerve conduction studies. In the correct clinical context, abnormalities of nerve conduction studies suggestive of patchy proximal and distal demyelination are highly suggestive of GBS. Nerve conduction tests may be normal in the first few days of illness. Typical changes of slowed motor nerve conduction velocities, with prolonged F-wave and distal motor latencies with largely preserved amplitudes are typical. Conduction block may be demonstrated. Early on the lower limb sensory action potentials are relatively preserved but they are later lost and electromyographic (EMG) evidence of denervation may emerge. Inexcitable nerves are common in severe cases and are unhelpful in diagnosis. Axonal changes without evidence of slowing are found in acute motor axonal and acute motor and sensory axonal neuropathies (AMAN and AMSAN) and these may indicate a worse prognosis.

Blood tests. Blood tests are unhelpful in the context of the diagnosis of GBS. However, they importantly serve to exclude major biochemical disturbances that may mimic GBS, identify coexistent disorders that may complicate treatment (e.g. renal failure and IVIG), and point to conditions that may cause a GBS-like illness (systemic lupus erythematosus [SLE], HIV, malignancy). All patients should have urea and electrolytes, calcium, magnesium, liver and thyroid function, full blood count, erythrocyte sedimentation rate (ESR), vitamin B$_{12}$ and folate and antinuclear antibodies (ANA) checked.

Ten per cent of patients will have abnormal liver function tests, possibly the result of viral (Epstein–Barr virus [EBV] or cytomegalovirus [CMV]) hepatitis. Hyponatraemia occurs in a proportion of patients caused both by syndrome of inappropriate antidiuretic hormone (SIADH) or an excess of atrial natriuretic factor.

Antiganglioside antibodies. Antiganglioside antibodies are frequently requested but seldom help in diagnosis. They are sometimes found more commonly associated with one or other of the regional GBS variants. In the acute neuropathies only IgG antibodies are of relevance. IgG anti-GQ1b antibodies are found in 90–95% of cases of Fisher syndrome and also a substantial proportion of cases of GBS with ophthalmoplegia. Anti-GD1a and anti-GalNAcGD1a antibodies are associated with AMAN. IgG anti-GM1 antibodies associate with more severe disease. Anti-GM2 antibodies sometimes follow CMV infection and seem to be associated with a predominantly sensory neuropathy. Ganglioside species share epitopes and therefore more than one antiganglioside activity is commonly found.

Campylobacter stool testing and serology. Serological testing with acute and convalescent serum may confirm seroconversion following infection with any of the infectious agents implicated in GBS causation. Stool should also be cultured for Campylobacter species. Its identification also has public health implications.

Lung function testing. Forced vital capacity (FVC) should be measured and recorded immediately on presentation and at least every 4 hours thereafter (more frequently if necessary) until the patient has begun to recover. Elective intubation should be considered if the FVC falls below 15 mL/kg.

Cardiac monitoring. A 12-lead ECG should be recorded and the patient monitored for arrhythmia and blood pressure fluctuations until stabilized and improving.

Nerve biopsy. Sural nerve biopsy is seldom helpful as much of the pathology in GBS is proximal and changes may take days to weeks to develop. In severe, unusual cases or cases unresponsive to treatment sural nerve biopsy may be helpful to exclude alternative diagnoses.

Variants of GBS

AMAN and AMSAN form a spectrum of axonal GBS. Although responsible for only 3–5% of cases of GBS in the western hemisphere, axonal variants may constitute up to 50% or more of GBS cases in China and South America. Here GBS occurs in seasonal summer outbreaks and is closely associated with *Campylobacter jejuni* infection. Anti-GD1a, GalNAcGD1a and GM1 antibodies occur frequently. The pathology involves direct macrophage attack on the axolemma resulting in profound axonal degeneration.

Limited and regional variants of GBS are shown in Table 9.9. Individual variants are rare but the combined incidence rate of all variants is about 7–13% of the incidence of GBS. Fisher syndrome, the triad of ataxia, areflexia and ophthalmoplegia is the most common variant accounting for between one-third and half of variant cases. There is a frequent association with *C. jejuni* infection. Up to 95% of cases are associated with anti-GQ1b antibodies. Fisher syndrome seldom progresses to require supportive or therapeutic treatment. Occasionally, a Fisher/GBS overlap syndrome or GBS with ophthalmoplegia may progress to full-blown weakness and thus it should be monitored and treated like GBS.

Other limited and regional variants are rare. The pharyngo-cervico-brachial variant involves predominantly the bulbar and upper limb musculature with weakness and areflexia but sparing the lower limbs. Anti-GT1a antibodies (sometimes cross-reacting with GQ1b) are often found. The pathophysiology is predominantly axonal. Paraparetic lower limb variants have been described as having pure motor and pure sensory or sensory ataxic forms. Acute dysautonomia has more recently been recognized in this group of conditions. It presents with profound postural hypotension and impaired sweating, impotence and bladder and bowel dysfunction. Antibodies to the nicotinic, ganglionic acetylcholine receptor have been described associated with this condition which improves with immunotherapy.

Pathogenesis

The infectious agents associated with GBS probably all display ganglioside-like epitopes on their surface. Immune responses to these epitopes cross-react with gangliosides displayed on nerve cells resulting in immune attack.

The pathogenic hallmark of typical GBS is macrophage-mediated attack of either the Schwann cell or the axolemma resulting in demyelination or axonal degeneration. The BNB becomes inflamed and leaky allowing for the ingress of activated T cells, IgG and complement. IgG and activated complement is found on actively degenerating cells. The inflammatory milieu stimulates up-regulation of MHC Class II receptors and antigen presentation by endoneurial cells including Schwann cells, promoting endoneurial damage.

Treatment

General treatment

1 Respiratory monitoring is essential. Elective endotracheal intubation may be life-saving with early conversion to tracheostomy for comfort and prevention of complications.

2 Cardiac monitoring in a high dependency unit setting should be performed in all patients while the diagnosis is being confirmed and until recovery begins. Arrhythmias and blood pressure fluctuations should be treated appropriately. Persistent or severe bradyarrhythmias may require the insertion of a pacemaker.

3 Anticoagulation (low molecular weight heparin), pressure stockings and calf massage devices as prevention against deep venous thrombosis (DVT) should be used routinely.

4 Fluid balance, nutrition and electrolyte monitoring. A nasogastric tube may be necessary for feeding, which may need to be supplemented. Hyponatraemia is more often brought about by excess atrial naturetic factor (ANF) (with loss of salt *and* water) than SIADH.

5 Physiotherapy should start immediately with hand and foot splints to prevent contractures.

6 Excellent nursing care of the paralysed patient prevents many complications associated with immobility and recumbency (pneumonia, pressure sores, DVT) and should be the central point of all care. Detection and treatment of issues related to pain, emotion, continence, nutrition and mouth care are crucial.

Specific treatment

Plasma exchange was the first GBS treatment shown to have substantial benefit. It halves the need for ventilation, hastens recovery and improves outcome at 1 year if administered within 4 weeks of onset. Usually 4–5 3-L exchanges are given over the course of 10 days. More practically, IVIG 2 g/kg over 5 days is as effective as plasma exchange and more likely to be completed as it has fewer complications. No additional benefit has been shown for following plasma exchange with IVIG. No trial has been performed to examine the benefit of a second dose of IVIG 14 days after the first in cases of minimal or delayed response. Steroids are not indicated in the treatment of GBS.

Pain may be severe. Treat with combinations of high-dose anticonvulsants (gabapentin, pregabalin, carbamazepine) and tricyclic antidepressants or selective serotonin re-uptake inhibitors (SSRIs), in conjunction with opiates (e.g. fentanyl). Epidural anaesthesia is sometimes helpful.

Outcome

Despite many advances in therapeutics and intensive care, GBS remains a severe illness. Poor prognostic factors include advanced age, axonal degeneration in the context of AIDP and if the patient is ventilator-dependent or bed-bound at the nadir of the illness. Even with the best medical care 5–8% of patients die and about one-third are left with significant disability. The remainder make a good recovery and have few residual symptoms. Fatigue is an under-recognized and poorly treated residual outcome.

Chronic inflammatory neuropathies

The chronic inflammatory neuropathies include the idiopathic and those associated with other diseases, e.g. the paraproteinaemias and the vasculitides (Table 9.9). Although the latter group, especially the vasculitides and paraneoplastic disorders, may present more acutely and progress more rapidly, they are included here for convenience.

Chronic inflammatory demyelinating polyradiculoneuropathy

CIDP is an acquired, treatable, demyelinating PNS disease characterized by progressive or relapsing proximal and distal weakness of the limbs with sensory loss and/or cranial nerve involvement reaching a nadir in more than 8 weeks with absent or reduced reflexes in all limbs. Prevalence estimates vary at 1.2–7/100,000 population. Unlike GBS there are no known predisposing infections.

Symptoms and signs

The diagnosis of CIDP is clinical, supported by electrophysiological, CSF and other tests (see below) and the exclusion of other causative pathologies.

Patients with CIDP present with a progressive or relapsing limb weakness or numbness which may have an asymmetrical onset. Parasthesiae are common. Limb and back pain occurs but if prominent should stimulate a search for alternative causes especially vasculitis, lymphoma or infection. As with all demyelinating conditions a tremor may be prominent. Autonomic and bladder or bowel involvement is distinctly unusual. 'Recurrent GBS' should be classified as CIDP. Unusual forms can occur including monomelic paralysis, lower limb variants and sensory ataxic forms.

The clinical signs mirror the presentation. Proximal and distal weakness with areflexia and a distal sensory loss are normal and tremor occurs frequently. Wasting is not evident until late in untreated disease. Progression to respiratory involvement and need for ventilation occurs rarely.

A careful general examination is crucial to identify systemic causes or contributing factors (e.g. malignancy, pre-existing CMT, SLE and other connective tissue diseases, diabetes or alcohol).

Investigations

The European Federation of Neurological Sciences and the Peripheral Nerve Society have published criteria for essential and supportive investigations.

1 *Nerve conduction studies.* Clear demonstration of demyelination in at least two nerves is mandatory for a definite diagnosis of CIDP if no other supportive criteria are employed. Demyelinating features of reduced motor conduction velocity, prolonged distal motor latencies or proximal F-waves or conduction block or dispersion, all in the presence of relatively preserved compound muscle action potentials are acceptable. Later in the condition axonal degeneration may supervene.

2 *CSF.* The CSF protein is raised in 90% of cases. A CSF white cell count of $>10\ \text{mm}^3$ should prompt a search for alternative causes.

3 *MRI.* Nerve root enlargement and/or enhancement with gadolinium is often seen. Most commonly imaged areas include the cervical and lumbosacral regions. MRI findings are now included in the supportive criteria for the diagnosis.

4 *Nerve biopsy.* A diagnosis of CIDP does not always require a nerve biopsy as the clinical presentation, neurophysiology and other less invasive paraclinical investigations are usually sufficient to make a diagnosis. Furthermore, complications include a 10–30% risk of permanent dysaesthesia at the biopsy site and other routine surgical complications of wound healing and infection. Although the sural nerve is the most commonly biopsied, a suitable nerve should be selected on the basis of symptoms and electrophysiological findings; only very rarely should an electrically 'normal' nerve be biopsied.

Biopsies contain reduced numbers of myelinated nerve fibres with evidence of active demyelination or previous onion bulb formation (Plate 9.3). Endoneurial macrophage activity is usually increased and endoneurial T cells are present in increased numbers. Unequivocal diagnostic findings in the correct clinical context are macrophage-associated demyelination on EM, evidence of demyelination or remyelination in five fibres by EM or demyelinated segments of at least 20 fibres in teased preparations.

5 *Blood tests.* There are no diagnostic blood tests for CIDP. Full blood count, ESR, B_{12} and folate, urea and electrolytes, glucose, liver and thyroid function tests, immunoglobulins, protein electrophoresis and immunofixation and ANA should be requested as an initial screen to rule out other conditions.

6 *Exclusion of other conditions.* Exclusion of other causative or contributing conditions is essential. Coexistent CMT disease should be considered and genetic tests requested as necessary.

CIDP variants

Multi-focal motor neuropathy with conduction block

Multi-focal motor neuropathy with conduction block (MMNCB) is a progressive immune-mediated demyelinating motor neuropathy which often begins asymmetrically in the upper limbs. Weakness in the distribution of individual nerves, often with prominent cramps but without wasting or fasciculation, and patchy reduced reflexes are the most usual signs. Wasting and fasciculation can occur later which causes confusion with motor neurone disease. Subjective sensory symptoms can occur but no more than minor disturbance of vibration sense at the ankle is acceptable on examination. Cranial nerve or respiratory involvement are extremely rare and upper motor neurone, sphincter or marked bulbar involvement exclude the diagnosis. The prevalence of MMNCB is about 10% of that of CIDP. Men are more often affected than women.

Both IgG and IgM antibodies to ganglioside GM1 are described in the serum from 30–80% of patients, rarely as a paraprotein. CSF protein should not be raised to >1 g/L. The hallmark of the condition is the demonstration of multi-focal conduction blocks at sites other than common sites of compression. Extremely thorough neurophysiological assessment may be necessary to identify them.

MMNCB was originally described in 1988 as a subtype of CIDP but it may be a distinct entity as illustrated by its dramatically different response to immunosuppressive therapy including worsening with steroids (see below).

Multi-focal acquired demyelinating sensory and motor neuropathy

Multi-focal acquired demyelinating sensory and motor neuropathy (MADSAM), previously called Lewis–Sumner syndrome, has similarities to CIDP and MMNCB. It may respond to treatment with IVIG.

Sensory ataxic CIDP

This rare inflammatory disorder presents with profound sensory ataxia and may be caused by inflammatory involvement of the dorsal root ganglia. HIV, paraneoplasia, Sjögren's syndrome, copper deficiency and pyridoxine toxicity should be excluded.

Distal acquired demyelinating sensory neuropathy

Many cases of distal acquired demyelinating sensory neuropathy (DADS) are associated with an IgM paraprotein.

Chronic relapsing axonal neuropathy

Chronic relapsing axonal neuropathy (CRAN) is a rare entity that has an uncertain position in the nosology of CIDP.

Treatment of typical CIDP

Treatment should be commenced as soon as possible in patients who warrant it after discussion of the risks and potential benefits with the patient. The first line treatments for CIDP are either oral steroids (although various regimens are used, 1 mg/kg given for 2 months and then slowly tapered is common) or IVIG (0.4 g/kg for 5 days repeated at 4–6 weeks and then as necessary according to the response). Both steroids and IVIG have been shown to be better than placebo and there is no clear difference between IVIG and steroids. Steroids should be co-prescribed with a bisphosphonate to protect against bone loss, and gastric pharmacoprotection should be considered. IVIG is a blood product and patients should be made aware of and consented for the risks. If IVIG or steroids are contraindicated or ineffectual then plasma exchange should be considered.

Other immunosuppressants have been tried in CIDP but cyclophosphamide is the only one to have shown promise.

MMNCB, MADSAM and possibly motor-predominant CIDP may deteriorate with steroids and therefore steroids should be avoided in these conditions.

Outcome

CIDP is a chronic progressive or relapsing disease. About 80% of patients will respond to treatment. Where patients fail to respond to treatment an occult paraprotein should be sought annually.

Over half (54%) of patients require assistance to walk or are bed-bound at some stage of their illness; 13% of patients require assistance to mobilize or are bed-bound at any one time. Over 50% require continuous treatment to maintain stability.

Paraproteinaemic neuropathies

Neuropathies associated with a paraprotein occur more often than by chance alone. The prevalence of a paraprotein in the serum at the age of 50 is approximately 1%, rising to 3% aged 70. Some 30–70% of patients with a paraprotein have a demonstrable peripheral neuropathy. Conversely, of a group of patients with no other identifiable cause for their neuropathy, 10% have a paraprotein. Most neuropathies are associated with 'benign' paraproteinaemias (monoclonal gammopathies of undetermined significance [MGUS]). Although IgG paraproteins account for 61% of all paraproteins, IgM MGUSs are over-represented in association with neuropathies and in many the MGUS is thought to be implicated in causation. Neuropathies associated with malignant gammopathies are more often caused by compressive lesions, direct infiltration or amyloidosis.

If a paraprotein is discovered in the serum it should be fully investigated with a full clinical examination, search for urine light chains, a skeletal survey and a bone marrow aspirate and trephine to establish whether it is benign or malignant. The differential diagnosis of gammopathies associated with neuropathy is shown in Table 9.9.

Neuropathies associated with IgM paraproteins

The neuropathy associated with IgM paraproteins is most frequently demyelinating. About 50–70% of the paraproteins react with the peripheral nerve epitope displayed by myelin-associated glycoprotein (MAG). A κ light chain is most frequent although IgMλ anti-MAG paraproteins do occur. The clinical picture associated with anti-MAG antibodies is relatively homogeneous. A slowly progressive distal sensorimotor neuropathy with a variable degree of ataxia and prominent tremor is typical. Men are affected more than women, with a mean age of onset of 59 years. The neurophysiological features are demyelination with characteristic prominent distal slowing. Nerve biopsy (not required for diagnosis) shows characteristic widening of the myelin lamellae (Plate 9.4).

There is good evidence to indicate that anti-MAG IgM paraproteins are pathogenic. The evidence for the pathogenesis of other IgM paraproteins is less robust even though other serum activities to specific epitopes are reported. Thus, when IgM paraproteins occur in conjunction with CIDP-like and axonal neuropathies they are treated accordingly (see below).

Neuropathies associated with IgG and IgA paraproteins

The neuropathy associated with an IgG or IgA paraprotein is most often a chronic symmetrical predominantly sensory neuropathy similar to CIDP, but the presentations are much more heterogeneous than for IgM. People with IgG and IgA MGUS neuropathy often have less weakness and relatively more sensory involvement, both clinically and neurophysiologically, than do people with idiopathic CIDP. Electrophysiologically the neuropathies are either demyelinating or axonal/mixed neuropathies in approximately equal numbers. Debate continues about whether a patient with an IgG MGUS and otherwise typical CIDP justifies a separate diagnosis.

Neuropathies associated with lymphoma/CLL/Waldenström's macroglobulinaemia

Neuropathy may be the presenting feature of a malignant gammopathy. A progressive painful neuropathy is common. Axonal and demyelinating large fibre and small fibre involvement occur. Several pathogenic mechanisms have been described including direct antibody attack on the nerves, immunoglobulin deposition, cryoglobulinaemic vasculitis, cold agglutinin activity, amyloid deposition, increased serum viscosity and ischaemia and direct infiltration by malignant cells (neurolymphomatosis).

POEMS syndrome

Polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes constitute the POEMS syndrome, a rare haematological paraneoplastic disorder in which the cytokine vascular endothelial growth factor (VEGF) is strongly implicated in the pathogenesis. All five clinical features are not always present at presentation. The minimal criteria to establish the diagnosis are the presence of a demyelinating and axonal polyneuropathy associated with an IgA or IgG monoclonal gammopathy, the light chain being almost always λ, and at least two of eight other features: sclerosing plasmacytoma, endocrinopathy, skin changes (of which glomeruloid haemangiomas are specific to POEMS), organomegaly, Castleman disease, generalized oedema, papilloedema or thrombocytosis. Ultrastructural identification of uncompacted myelin lamellae on the peripheral nerve biopsy is also a strong argument in favour of the diagnosis.

Cryoglobulinaemic neuropathy

See vasculitis below.

Neuropathies associated with multiple myeloma, solitary myeloma and other malignant plasma cell dyscrasias

The neuropathies associated with a malignant plasma cell dyscrasia are heterogeneous. They should be managed in conjunction with a haematologist.

Treatment of paraproteinaemic neuropathies

Because the neuropathy associated with paraproteinaemia is often mild and only slowly progressive treatment may not be required. The level of paraprotein and the neuropathy should be monitored as there is a risk of approximately 1% per year of malignant transformation of the B-cell clone. Treatments are aimed at reducing the amount or activity of antibody in the serum. IVIG has short-term benefit in IgM paraproteinaemic neuropathies. Rituximab is showing promise as an effective treatment. Plasma exchange, steroids, chlorambucil, azathioprine, cyclophosphamide, α-interferon, fludarabine and cladribine have all been used with variable success. For IgG and IgA paraproteinaemic neuropathies those with a slowly progressive distal axonal polyneuropathy tended to show a poor response to immunotherapy. Patients with a sensorimotor demyelinating neuropathy tend to respond better. In POEMS syndrome, specific treatment of osteosclerotic bone lesions may improve the other features of the syndrome, especially the neuropathy. Autologous bone marrow transplantation has been effective in some.

Acquired amyloid neuropathy

In AL (light chain) amyloidosis the constituent amyloid protein is derived from monoclonal immunoglobulin light chains secondary to multiple myeloma, malignant lymphoma or Waldenström's macroglobulinaemia, or to a non-malignant immunocyte dyscrasia. Amyloid develops in approximately 15% of patients with myeloma and less frequently in other malignant B-cell disorders.

The amyloid is more commonly derived from λ than κ light chains.

Clinical features

The incidence of AL amyloidosis is 5.1–12.8 per million. Light-chain amyloidosis occurs predominantly in later life, two-thirds between the ages of 50 and 70. It may present with non-specific symptoms such as malaise, fatigue and weight loss or with system specific symptoms, the most common being nephrotic syndrome, congestive cardiomyopathy, peripheral neuropathy (sometimes with autonomic involvement) and hepatomegaly. Associated features include purpura, oedema, hepatosplenomegaly and macroglossia.

Patients with neuropathy present with an acquired length dependent sensory loss with prominent small fibre involvement. Pain is often burning, especially nocturnally, or lancinating stabs. Autonomic involvement including distal limb anhydrosis, orthostatic hypotension, difficulty in voiding urine, and erectile and ejaculatory difficulty tends to be an early manifestation. Diarrhoea and gastroparesis may be prominent but whether this is related to direct gut wall or autonomic infiltration is uncertain.

On examination, nerves may be thickened, pain and temperature are selectively involved and autonomic involvement is often evident (including pupillary involvement).

Pathology

The pathological features of AL amyloidosis are similar to those already described in the section above on pathology of transthyretin-related FAP.

Diagnosis

Histological confirmation of amyloid deposition in nerve, rectum, abdominal fat or other tissue with Congo red is described above. Immunohistochemical staining for λ or κ light chains has a sensitivity of only 50%.

Once the diagnosis of AL amyloidosis is made it is necessary to screen for a paraprotein. Protein electrophoresis will detect a paraprotein in serum or urine in about 50% of patients where it is present. Immunofixation of serum and urine should be routinely performed and quantification of free light chains detects abnormality in 92% of patients. If all of the above techniques are used the sensitivity is 99%.

Bone marrow aspirate with a trephine biopsy and detailed systemic investigation should then be undertaken to assess the degree of other organ involvement, especially renal, cardiac and gastrointestinal. A serum amyloid protein scan identifies and quantifies tissue deposits in many tissues but not peripheral nerve.

Treatment of amyloid neuropathy

Symptomatic treatments for pain, autonomic symptoms and the neuropathy can be tried as outlined above for TTR-related FAP. Extensive cardiac or renal involvement may merit organ transplantation. Chemotherapeutic regimens of different intensity are available to treat patients diagnosed at different stages of their disease. It is very important that patients are treated by centres with expertise in amyloidosis as regimes are continually being researched and updated.

Prognosis

Prior to recent advances in treatment a median survival time of 35 months for patients with acquired amyloid peripheral neuropathy compared to 16 months for those without neuropathy was typical although longer survival is reported. Death was usually because of involvement of systems other than the peripheral nerves.

With treatment the outcome is better; a recent review reported that 22% of patients survived more than 10 years.

Vasculitic neuropathies

The vasculitic neuropathies are uncommon but are some of the most devastating treatable peripheral neuropathies. The principal pathology is vascular inflammation in the vessels of the vasa nervorum with fibrinoid necrosis and occlusion of the vessel leading to nerve infarction. The early recognition, diagnosis and appropriate treatment can prevent considerable morbidity. They can be classified into systemic or non-systemic and then into primary or secondary causes (Table 9.9).

Symptoms and signs

Sequential progressive painful sensorimotor mononeuropathies presenting over days or weeks is typical of the presentation of vasculitis. Lower limb nerves tend to be affected first. Progression to confluence occurs, especially in polyarteritis nodosa (PAN) and Wegener's granulomatosis, and more slowly in some of the secondary vasculitides. Systemic involvement may present as fever, weight loss, myalgia, fatigue and night sweats or as organ-specific symptoms of rash, wheeze or shortness of breath, haematuria and arthritis or arthralgias.

Primary vasculitides

1 *Churg–Strauss syndrome.* Up to 80% of patients with Churg–Strauss syndrome present with a neuropathy. Fever, pulmonary infiltrates, late onset asthma, skin rash and eosinophilia are often all present. Antineutrophil cytoplasmic antibody (ANCA) is positive in up to 70%.

2 *Wegener's granulomatosis.* This is a midline necrotizing vasculitis associated with a positive c-ANCA in 90% of patients. A neuropathy occurs in up to 40% of patients and may be confluent.

3 *Polyarteritis nodosa.* True PAN is rare. It affects muscular arteries and arterioles only and is ANCA negative. Neuropathy occurs in 75% of cases and presents quite frequently as a painful symmetrical picture. Hepatitis B infection is often associated and implicated in the genesis.

4 *Microscopic polyangiitis.* This is an overlap syndrome in which neuropathy occurs in 50–60% of cases. p-ANCA is often positive.

Secondary vasculitides

1 *Rheumatoid arthritis* (RA). The most common neuropathy associated with RA is a slowly progressive distal symmetric sensory neuropathy, many of which are asymptomatic. This is not vasculitic. Vasculitic neuropathies occur more often in late seropositive disease.

2 *SLE.* This may present with a multiple mononeuropathy with vasculitis on nerve biopsy. However, a CIDP or GBS-like illness also occurs.

3 *Infection.* Hepatitis C is strongly associated with the presence of type II (mixed) cryoglobulinaemia. This is associated with a painful asymmetric multiple mononeuritis. The treatment is that of hepatitis C with ribavarin and interferon, although there are a number of case reports of vasculitis occurring in association with treatment per se.

Vasculitis directly attributable to HIV occurs in <1% of cases. More frequent is a vasculitis secondary to coexistent hepatitis B (see above), CMV or lymphoma.

Non-systemic vasculitides

1 Non-systemic vasculitic neuropathy usually has a more subacute or chronic course, but again with multiple mononeuropathies. Systemic symptomatic features are absent, except occasionally weight loss or fevers. No other organ involvement is identified on investigation. The prognosis and response to treatment are more favourable than with systemic forms.

2 Diabetic lumbosacral plexopathy (diabetic femoral neuropathy, Bruns–Garland syndrome, diabetic amyotrophy). There remains controversy about the classification of this entity but there it seems to be a monophasic vasculitis.

Investigation of vasculitic neuropathies

1 *Haematological and biochemical investigation*. Routine investigations should include full blood count, ESR, urea and electrolytes, C-reactive protein (CRP), liver and thyroid function, glucose (+/− HbA1c), ANA, ANCA, rheumatoid factor and RA latex, complement, serum protein electrophoresis and immunofixation, cryoglobulins (transfer to the laboratory at 37°C), hepatitis B and C. Consider requesting anti-ENA (extractable nuclear antigen), anti-CCP (cyclic citrullinated peptide), serum ACE (angiotensin converting enzyme), HIV testing and Lyme serology.

The urine should be examined for red cell casts and Bence-Jones proteinuria.

2 *Radiology.* A chest X-ray should be performed.

3 *CSF* is not usually helpful in vasculitic neuropathies. It should be performed to rule out differentials including HIV, carcinomatosis, lymphoma and Lyme disease.

4 *Neurophysiology*. Patchy asymmetric sensorimotor axonal damage is typically found with evidence of acute or subacute denervation on EMG. Demyelinating neuropathies are sometimes found but should point to alternative or additional pathologies.

5 *Nerve biopsy.* Patients with vasculitis are likely to need treatment with high dose, potentially toxic immunotherapies for a considerable time. A biopsy-proven diagnosis can usually only be made before treatment commences and it will reassure both physician and patient about their treatment. A biopsy of skin, liver, kidney or lung might be alternatives. If a nerve biopsy is performed, a recently affected sensory nerve should be selected. Biopsy of the superficial peroneal nerve and the underlying peroneus brevis muscle increases the chances of diagnosis over biopsy of the superficial peroneal nerve alone.

Patchy axonal fibre loss with active axonal degeneration is frequently seen in vasculitides. The diagnostic hallmarks of T-cell infiltration into vessel walls with destruction of the elastic lamina and fibrinoid necrosis with vessel occlusion (Plate 9.5) are seen less frequently. Biopsies should be carried out by an experienced surgeon and interpreted by a histopathologist with specific experience in peripheral nerve disease.

Treatment

The vasculitides are a treatable group of disorders because of the ischaemic pathology; missing the opportunity to treat early may result in permanent irrecoverable peripheral nerve lesions. Randomized controlled trial evidence for specific therapeutic regimens does not exist.

Non-virus-associated vasculitis

Treatment is usually required, except in mild or non-progressive cases (usually non-systemic vasculitic neuropathy) and usually urgently. The key to treatment is the initial induction of remission followed by a maintenance phase. Oral steroids at a dose of 1–2 mg/kg or pulsed methylprednisolone (monthly courses 1 g/day for 3–5 days with 1 mg/kg oral prednisolone between) are usual. Wegener's granulomatosis and microscopic polyangiitis often require a more aggressive treatment course than Churg–Strauss or the non-systemic vasculitides. However, each case should be judged on its merits. Furthermore, there is good retrospective evidence that the addition of additional agents to the remission regimen improves the rate of remission, disability at 1 year and the rate of relapse even in non-systemic vasculitis. Cyclophosphamide is the most commonly used agent. Oral cyclophosphamide (2 mg/kg/day) is traditionally used; however, many clinicians now prefer to use monthly pulsed intravenous cyclophosphamide (10–15 mg/kg, maximum 1 g per dose and modified by age and renal function) with prehydration and mesna cover for 6 months because of its reduced side effect profile.

Many agents have been used for maintenance which usually covers the tail of oral steroids and continues to 2 years depending upon outcomes and patient tolerance. Methotrexate, azathioprine, mycophenolate and leflunomide have all been shown to be beneficial in case reports. Rituximab is useful in cryoglobulinaemic and lymphoma-associated vasculitis and has shown promise in other primary vasculitides resistant to first line interventions.

Virus-associated vasculitis

Hepatitis B associated PAN responds to a short (2-week) induction course of steroids followed by a 6 months of antiviral treatment, either interferon-2α or lamivudine. Hepatitis C cryoglobulin associated vasculitis is treated with pegylated interferon-2α with ribavarin, although neuropathy has on occasion been induced when this regimen is used to treat hepatitis C alone. Plasma exchange is traditionally used alongside the treatment for both viruses to clear circulating immune complexes but is of no demonstrable benefit.

Outcome

Untreated vasculitis has a very poor outcome. In most types of vasculitis induction and maintenance treatment is associated with partial or complete recovery in about 50% of patients over months to years. Non-systemic vasculitis has much the best prognosis.

Other acquired peripheral nerve disorders

Endocrine disorders

Diabetes

Neuropathies occur extremely frequently in association with diabetes and, after leprosy, diabetes is the most common cause of neuropathy worldwide. Many neuropathies are asymptomatic or minor. Most occur later in the course of the disease; the prevalence of neuropathy is 50% after 25 years. The risk of neuropathy increases with duration of disease, poor control, height, male sex and with other cardiovascular risk factors constituting the 'metabolic syndrome'. Diabetic neuropathies can be classified as in Table 9.11.

Distal symmetric sensory neuropathy

Distal symmetric sensory neuropathy (DSSN) is the most common of the diabetic neuropathies. It presents with a slowly progressive 'glove and stocking' sensory loss which may be painful. Small fibre symptoms may also be present. With severe neuropathy, neuropathic Charcot joints may be present (Plate 9.6).

It is rarely necessary to perform a sural nerve biopsy on someone with apparently uncomplicated DSSN. Many of the biopsy features are non-specific but reduplication of basement membranes (Figure 9.12) and other endothelial alterations are commonly found.

Table 9.11 Classification of diabetic neuropathies.

Distal symmetric sensory neuropathy (DSSN)
Autonomic neuropathies
Vasculitic plexopathies and thoracolumbar radiculopathies (amyotrophies)
Focal and multifocal mononeuropathies
Small fibre neuropathy
Acute reversible hyperglycaemic neuropathy
Insulin neuritis and hypoglycaemic neuropathies
Neuropathies associated with diabetes, e.g. CIDP

CIPD, chronic inflammatory demyelinating polyradiculoneuropathy.

The pathophysiology is poorly understood but relates to prolonged periods of hyperglycaemia increasing flux through the polyol pathway. Increased metabolic and oxidative stresses result in advanced glycated end-products in nerve.

There is no effective treatment but progress of the neuropathy can be largely arrested with aggressive diabetic control, although this is only achieved in about 25% of patients. Pain can be treated with antiepileptic and antidepressant medication.

Autonomic neuropathies

These occur in both type I and II diabetes but are often most severe in type I. Diabetes is the most common cause of autonomic neuropathy in the West. Up to 75% of men have impotence. Gastrointestinal motility disorders are common with constipation and nocturnal diarrhoea. Subclinical cardiovascular autonomic involvement is common with sympathetic and parasympathetic cardiac denervation demonstrated by fixed high heart rates. Postural hypotension is demonstrable in more than 40% of patients but is seldom symptomatic.

Vasculitic plexopathies

The most common plexopathy is the diabetic lumbosacral plexopathy (also known as diabetic femoral neuropathy, diabetic amyotrophy, lower limb asymmetric motor neuropathy or Bruns–Garland syndrome). It presents with asymmetric aching pain in the buttock, hip or thigh followed by progressive weakness and wasting affecting the hip flexors and quadriceps. The knee jerks are lost but sensory loss is unusual unless there is a coexistent DSSN. Patients present with a progressive history of asymmetric leg ache or pain followed by weakness and wasting mostly in the femoral compartment. Usually, dramatic weight loss and the appearance of diabetes or worsening of its control are prominent.

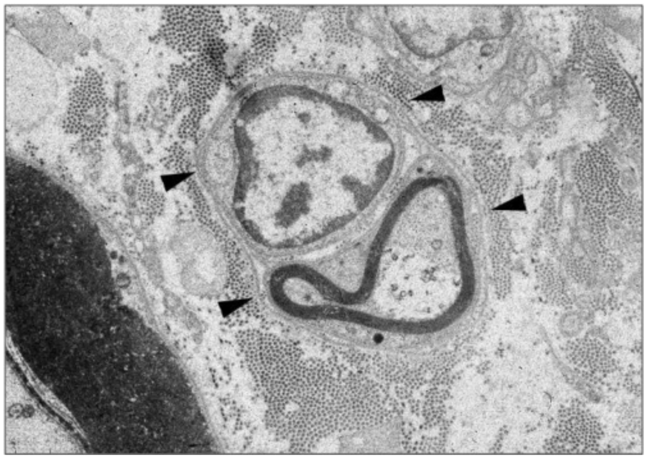

Figure 9.12 Diabetic nerve demonstrating reduplication of the basal lamina (arrows) around a Schwann cell and myelinated nerve fibre (case of DSSN).

Cervical plexopathies and thoracolumbar radiculopathies have also been described. These probably have the same pathogenesis.

Nerve conduction studies show radicular neurogenic changes in the quadriceps muscles. Pathological studies have suggested that this is a microvasculitis.

Regaining tight control of the diabetes is the basis of treatment. Both IVIG and pulsed intravenous and oral steroids have been anecdotally been said to be of benefit. However, spontaneous recovery (which is sometimes complete) may occur over 18–24 months without any treatment.

Focal and multifocal mononeuropathies

Individual mononeuropathies including carpal tunnel syndrome and peroneal neuropathies are more common in diabetes than in the healthy population because nerves are more susceptible to the mechanical effects of compression.

Cranial nerve palsies, most commonly pupil-sparing 'microvascular' IIIrd nerve palsies, are not uncommon. The VIIth and VIth nerves may also be affected.

Small fibre neuropathy

See below.

Acute reversible hyperglycaemic neuropathy

In patients with uncontrolled hyperglycaemia, an uncomfortable mainly lower limb sensory neuropathy can develop acutely. Nerve conduction is slowed. The symptoms resolve with reversal of the hyperglycaemia.

Insulin neuritis

Rarely, an acute painful neuropathy may develop after the introduction of insulin, leading to rapid normalisation of glycaemic control. There is scant evidence to support a pathology but a pre-existing diabetic neuropathy may be unmasked with sudden relative hypoglycaemia. Prognosis is good if insulin therapy is continued.

Neuropathies associated with diabetes (e.g. CIDP)

CIDP, but not GBS, is more common in diabetics than the otherwise healthy population. Severe proximal and distal diabetic neuropathy should be investigated for supra-added CIDP.

Hypoglycaemia

Recurrent and severe hypoglycaemia, as occurs in insulinoma, results in a distal symmetric sensorimotor neuropathy. Distal painful parasthesiae are usually prominent. Correction of the hypoglycaemia by treatment of the insulinoma results in improvement of the sensory symptoms but not the motor.

Hypothyroidism

Frank hypothyroidism is associated with a sensory axonal neuropathy in a substantial number of cases. Carpal tunnel syndrome occurs frequently as a presenting feature.

Acromegaly

Unrecognized and untreated acromegaly is now unusual. Most commonly weakness is caused by myopathy. CTS is common as are other entrapment neuropathies partly through hypertrophy of nerves. A distal predominantly sensory axonal neuropathy also occurs.

Toxic, nutritional and metabolic peripheral neuropathies

Toxic neuropathies

Peripheral nerve is relatively sensitive to the effects of systemic toxins (Chapter 18). The number of implicated drugs, chemicals and neurotoxins is too numerous to discuss each individually (Table 9.12). The reader is referred to http://www.neuro.wustl.edu/neuromuscular for a discussion of individual toxins.

If toxin exposure is suspected a full history and examination should be performed and a sample of the toxin should be retrieved if possible. Serum and urine specimens should be collected and, for acute poisoning, an Acute Poisons Unit consulted.

Most toxins cause axonal neuropathies, some of which have motor or sensory predominance. Fewer toxins cause demyelination. Frequently, the severity of the neuropathy is dose related. Removal of the source of the toxin may result in recovery which may be complete. Some agents 'coast' (i.e. the neuropathy tends to continue to worsen) for several weeks or months after removal of the toxin. Heavy metal poisoning may require specific treatment (e.g. lead, mercury and thallium) and toxins (e.g. α-latrotoxin, botulinum toxin) may benefit from antitoxin therapy. Prolonged supportive therapy in ITU may be required (e.g. botulism, tick paralysis).

Nutritional

Vitamin deficiencies occur through inborn errors of metabolism (e.g. vitamin E deficiency, methylcobalamin deficiency; Chapter 18), limited dietary intake (vegan/vegetarian diet, alcoholism) or failure of absorption (post-ileal resection, pancreatic failure, coeliac disease). Deficiencies may therefore be isolated or combined. Neuropathies are invariably axonal some associated with pain or ataxia and many with CNS involvement. Replacement of deficient vitamins by supplementation or providing an alternative metabolite can halt and sometimes improve the neuropathy.

Multi-vitamin malabsorption syndromes

1 *Coeliac disease.* Coeliac disease is associated with a typical length-dependent sensory neuropathy, sometimes with pain. As well as the systemic disease features, coeliac has also been associated with seizures, ataxia, myopathy, headaches and vitamin A deficient night-blindness. Causation is difficult to prove except in the latter.

2 *Inflammatory bowel disease.* Occasionally, a neuropathy occurs proportionate to the severity of the illness. Vitamin B_{12} deficiency through terminal ileal malabsorption is common.

3 *Cuban epidemic neuropathy* (Strachan's syndrome). Strachan's syndrome was described in prisoners of war. Cuban epidemic neuropathy occurs in patients of Afro-Caribbean origin and is

Table 9.12 Toxic neuropathies. After http://www.neuro.wustl.edu/neuromuscular

Axonal				
Sensory	**Sensory and motor**	**Motor**	**Demyelinating**	**Mixed**
Bortezomib	Acrylamide	β-bungarotoxin	Buckthorn	Amiodarone
Chloramphenicol	Alcohol (ethanol)	Botulism	Chloroquine	Ethylene glycol
Dioxin	Allyl chloride	Dimethylamine borane	Diphtheria	1,1′-Ethylidinebis [tryptophan]
Doxorubicin	Arsenic	Gangliosides	FK506 (tacrolimus)	
Ethambutol	Cadmium	Latrotoxin (Black widow spider venom)	Hexachlorophene	Gold
Ethionamide	Carbon disulphide	Lead	Muzolimine	Hexacarbons
Etoposide	Ciguatoxin	Mercury	Perhexiline	n-Hexane
Gemcitabine	Colchicine	Misoprostol	Procainamide	Na^+ cyanate
Glutethimide	Cyanide	Tetanus	Tellurium	Suramin
Hydralazine	Dapsone	Tick paralysis	Zimeldine	
Ifosfamide	Dichloroacetate			
Interferon-α	Disulfiram			
Isoniazid	DMAPN (foams)			
Lead	Ethylene oxide			
Leflunomide	Heroin			
Metronidazole	Lithium			
Misonidazole	Methyl bromide			
Nitrous oxide	Nitrofurantoin			
Nucleosides	Organophosphates			
ddC; ddI;	Podophyllin			
d4T; 3TC	Polychlorinated biphenyls			
Phenytoin	Saxitoxin			
Platinum analogues	Spanish toxic oil			
Propafenone	Taxol			
Pyridoxine	Tetrodotoxin			
Statins	Thallium			
Thalidomide	Trichloroethylene			
	Tri-ortho-cresyl phosphate			
	Vacor (PNU, a rat poison)			
	Vinca alkaloids			

very similar. It is thought to be caused by deficiencies in B vitamin and sulphur compounds. It typically occurs between 25 and 65 years of age with no sex predominance. Risk factors include tobacco and cassava consumption. The neuropathy is distal, axonal, sensory and often painful and occurs with an optic neuropathy presenting as central scotomata. Early treatment with B and multivitamin preparations can lead to resolution of the neuropathy although visual field defects may persist.

4 *Post gastroplasty/gastrectomy.* Patients may become malnourished through severely reduced dietary intake, diversion, bypass or resective procedures and sometimes vomiting. Copper and selenium deficiency may occur. Polyneuropathy, mononeuropathies (especially carpal tunnel), radiculopathies and myelopathies are all described.

Vitamin deficiencies

1 *Vitamin B_1* (beri-beri). Beri-beri presents with an acute or chronic length dependent sensorimotor axonal neuropathy primarily affecting the legs. Burning feet with lancinating pains are common as is autonomic involvement in severe disease. Wernicke–Korsakoff syndrome, cerebellar degeneration and cranial nerve palsies also occur as well as the systemic features of beri-beri (heart failure, oedema and weight loss).

2 *Pyridoxine* (vitamin B_6). In excess, pyridoxine typically causes a neuropathy/neuronopathy syndrome. Deficiency causes a length-dependent polyneuropathy. Users of isoniazid, penicillamine and hydralazine as well as alcoholics, the elderly and the malnourished are all at risk and should be supplemented appropriately.

3 *Vitamin B_{12}.* The causes of B_{12} deficiency are legion and all neuropathy blood profiles could include the measurement of B_{12} and folate. Symptoms are compounded by central and peripheral involvement. Deficiency may be long-standing and chronic. Nitrous oxide dental anaesthesia may unmask it. Typically, large fibre modality distal sensory loss begins first and motor involvement occurs later. Corticospinal tract involvement may lead to pyramidal weakness and extensor plantar responses. Treatment with vitamin B_{12} may stabilize or improve the neuropathy but seldom improves the central involvement.

4 *Vitamin E.* Deficiency states cause a distal axonal neuropathy associated with cerebellar and posterior column involvement. Plantar responses may be extensor.

Metabolic neuropathies

Porphyrias

Acute intermittent porphyria (AIP), coproporphyria, variegate porphyria and δ-amino-levulinate dehydratase porphyria cause neurological syndromes. The most common is AIP.

AIP typically occurs in attacks, affecting women more than men. Abdominal pain and constipation reflect the sympathetic and parasympathetic involvement which can cause great management difficulties with additional cardiovascular instability. The neuropathy is motor and sensory and may be severe enough to result in respiratory failure and require ventilation.

Nerve conduction studies typically show axonal degeneration with denervation and small sensory potentials.

Treatment of attacks is with haem arginate or haematin and supportive measures to treat pain, constipation and weakness (including ventilation).

Uraemic neuropathy

Renal failure, uraemia and dialysis are all associated with a multifactorial neuropathy. Up to 60% of patients have a subclinical neuropathy. Symptoms and signs are of a length dependent sensory axonal neuropathy occasionally with pain and prominent itching. Recovery from renal failure or renal transplantation may improve or reverse the symptoms.

Critical illness neuromyopathy (Chapter 19)

The existence of a severe critical illness neuropathy in the absence of a myopathy is controversial. Most patients who have a period of intensive care will have a mild distal sensory neuropathy following it. However, some patients have a severe proximal and distal weakness, sometimes affecting ventilation and weaning because of a myosin loss myopathy. This is most common in sepsis, dialysis-dependent renal failure and myasthenic crises as well as severe ITU episodes. On examination patients may be profoundly weak (including neck flexors), have absent reflexes and they often have distal sensory loss. Small compound muscle action potentials (CMAPs) are found on electrophysiology because of muscle inexcitability rather than axonal loss. Myosin is depleted in muscle biopsy specimens. Treatment is supportive.

Small fibre neuropathies

Small fibre neuropathies (SFN) are an increasingly recognized and symptomatically troublesome group of disorders with diverse causation. There are no studies of the epidemiology of SFN. This is largely because of the lack of a satisfactory definition for SFN and standardized methods of investigation and detection. A reasonable definition is 'a neuropathy characterized by positive (spontaneous or stimulus-induced) or negative sensory symptoms caused by dysfunction of Aδ or C fibres with or without autonomic abnormalities as assessed by specific neuropathological or electrophysiological tests'. Asymptomatic small fibre involvement may also occur in certain conditions.

The list of causes of SFN is increasing (Table 9.13). Unfortunately, perhaps 50% or more small fibre neuropathies have no identifiable cause.

Table 9.13 Small fibre neuropathies.

Idiopathic
Idiopathic small fibre neuropathy
Recognized syndromes (e.g. burning mouth, burning feet, Ross syndrome, rectal hypersensitivity, vulvodynia)

Metabolic
Diabetes mellitus
Impaired glucose tolerance
Hyperlipidaemia

Toxic
Alcohol
Metronidazole
HAART
Statins
Environmental and marine toxins

Infective
HIV
EBV
Leprosy
Chagas disease
Botulism

Immune
Associated with MGUS
Paraneoplastic
Sjögren's syndrome
Sarcoidosis
SLE
Inflammatory bowel disease

Hereditary
Fabry's disease
Tangier disease
Hereditary sensory and autonomic neuropathies (especially HSAN I, IV and V)
Familial amyloid polyneuropathy
Familial burning beet

Systemic amyloidosis

EBV, Epstein–Barr virus; HAART, highly active antiretroviral therapy; MGUS, monoclonal gammopathies of undetermined significance; SLE, systemic lupus erythematosus.

Symptoms

Small fibre neuropathies most often present with positive sensory symptoms of pain (often burning, pricking or aching) in the feet. Sometimes the symptoms also affect the upper limbs. Pain may be spontaneous or stimulus evoked. It is often worse at night, may interfere substantially with sleep, and can be relieved temporarily by walking or immersing the feet in cold water. Lancinating pain and paraesthesiae are usually indicative of additional large fibre involvement.

An association with restless legs syndrome is not uncommon. Significant autonomic disturbances are uncommon in idiopathic small fibre neuropathy and most often mild. Prominent orthostatic hypotension, faecal urgency, diarrhoea (especially nocturnal) and incontinence, urinary difficulties, impotence and sweating abnormalities should all prompt a search for diabetes, amyloid, vasculitis or a hereditary cause.

Signs

The allowable clinical signs in SFN vary between authors. Usually there is reduced temperature and pain sensation in the distal feet. Otherwise there should be no muscle wasting or weakness, deep tendon reflexes should be present and bedside vibration and proprioception should be normal.

Investigation

Causation should be sought with appropriate blood tests and chest X-ray. Standard nerve conduction tests are normal. Thermal threshold testing (especially warm thresholds which correlate well with intra-epidermal nerve fibre densities) is a low resolution but effective method to confirm the diagnosis. Other tests are being developed (contact heat evoked potentials [CHEPs], laser evoked potentials [LEPs], measurement of cutaneous silent periods and axon reflex flare responses) but are yet to be fully validated or widely used. Skin biopsy is a useful, largely painless, site specific and minimally morbid procedure to quantify intraepidermal nerve fibre density with high diagnostic efficiency and predictive value. Sural nerve biopsy does not form part of the investigation of small fibre neuropathy.

Treatment

No treatments are yet available to treat or reverse small fibre neuropathy. Erythropoietin has shown promise in limited *in vitro* scenarios. Treatment is largely symptomatic and trials of gabapentin, pregabalin, sodium valproate, topiramate and opiates all demonstrate some benefit. Tricyclic antidepressants, duloxetine, oxcarbazepine and others are often tried. Enzyme replacement is helpful for the small fibre neuropathy in Fabry's disease.

Idiopathic axonal neuropathy

Despite best practice the cause of at least 25% of neuropathies remain undiagnosed. These are largely a group of slowly progressive but usually non-disabling axonal and small fibre neuropathies. Careful history-taking, examination and sometimes the ability to examine 'unaffected' relatives improves diagnosis. Over the coming years many of these conditions will be diagnosed more successfully.

Focal and compressive neuropathies

Focal neuropathies are the result of local damage to individual nerve trunks. They may be single or multiple; the occurrence of more than one pressure palsy should stimulate a search for a predisposing cause. Damage occurs most frequently because of compression, usually as the nerve passes through a tissue tunnel (bone, ligament, aponeurosis, muscle), or against an underlying surface at an exposed site (e.g. the peroneal nerve as it passes around the head of the fibula). Compression may also occur with prolonged abnormal postures (e.g. radial paralysis in the 'Saturday night palsy'). Diabetes, HNPP and alcohol overuse render nerves susceptible to the effects of otherwise non-damaging pressure.

The pathogenesis of focal compressive nerve dysfunction is probably multi-factorial and in experimental studies the mechanisms of acute and chronic compression have been shown to differ. At sites of acute compression endoneurial fluid, axonal contents and subsequently myelin are squeezed down the pressure gradient at the edge of the compression, resulting in nerve intussusception and subsequently Wallerian degeneration. In chronic compression, focal demyelination is found with alterations in nodal structure suggestive of a 'myelin slippage' secondary to stretching. In addition, endoneurial ischaemia may occur and contribute to focal pathology. The transperineurial venous plexus may be easily compressed as it obliquely exits the perineurium resulting in increased endoneurial tissue pressures, reduced blood flow and alteration in the endoneurial metabolic microenvironment. Over the longer term, impaired axonal transport may result in reduced distal trophic support. Furthermore, a nerve that becomes tethered at a site of inflammation can become further damaged; the inability of the nerve to glide during limb movement results in more nerve stretching.

Compression palsies cause signs in the motor and sensory distribution distal to the site of compression. Symptoms may occur both proximal and distal to the site. The reader is referred to diagrams of neuromuscular innervation at the beginning of this chapter (Figures 9.3–9.6). The most common focal neuropathies affect the median (carpal tunnel syndrome), ulnar and common peroneal nerves. Many other nerves may be affected producing a variety of syndromes, many with colloquial names (e.g. orator's [anterior interosseous] and claw [ulnar] hand, waiter's tip and Saturday night [radial] palsy in the upper limb and toilet seat [sciatic], strawberry and turnip picker's and hoeing [peroneal] palsies in the lower limb). These are not always entirely 'typical' as anatomical variations may vary muscle and cutaneous innervation (e.g. Martin–Gruber anastomoses between median and ulnar nerves). Lesions of any other individual nerve trunk are possible and result in motor and/or sensory signs in the distribution of their innervation. The most common are the lateral cutaneous nerve of the thigh (resulting in meralgia paraesthetica), sciatic,

Table 9.14 Other focal neuropathies.

Colloquial terminology	Sites of compression	Weakness	Sensory loss
Upper limb			
Median nerve			
Carpal tunnel syndrome (CTS)	Wrist (carpal tunnel)	Opponens pollicis, abductor pollicis brevis, flexor pollicis brevis, lumbricals	Palmar skin of thumb, digits II, III (and lateral IV)
Circle sign	Anterior interosseous nerve (below elbow)	Flexor pollicis longus and flexor digitorum profundus (median) – the circle sign	None
Orator's hand	Bicipital aponeurosis (elbow), or Ligament of Struthers (above elbow)	Median innervated flexors (profundus/superficialis) and pollicis + pronators quadratus and teres	Palmar + CTS loss
Ulnar nerve			
Guyon canal syndrome	Guyon canal at wrist	Interossei and abductor digiti minimi (variable)	Distal superficial ulnar (variable)
'Claw hand'/tardy ulnar palsy/cubital tunnel syndrome	Elbow	As above + flexor carpi ulnaris, flexor digitorum profundus (ulnar)	Medial surface of palm and digits V and IV
Radial nerve			
Waiter's tip palsy	Upper arm/axilla	Triceps (strong in proximal lesions), brachioradialis, wrist and finger extensors	Superficial radial territory of hand (snuff box)
Tourniquet palsy			
Saturday night palsy			
Crutch palsy (sometimes with ulnar and median = *triad* neuropathy)			
Wartenberg syndrome	Wrist	None	
Cheiralgia paraesthetica			
Axillary nerve	Axilla or humeral head	Deltoid	Skin over deltoid
Suprascapular nerve			
Pitcher's neuropathy	Suprascapular notch or ligament	Supra- and infraspinatus weakness (often painful)	None
Long thoracic nerve			
Rucksack palsy	Shoulder or lateral thoracic wall	Serratus anterior	None
Long thoracic neuropathy			
Brachial plexus			
Neurogenic thoracic outlet syndrome	C7 transverse process, anterior scalene muscle, fibrous band	C8 root > T1 root hence thenar > hypothenar muscles	Ulnar border of hand, forearm and arm
Lower limb			
Sciatic nerve			
Toilet seat palsy	Gluteal compression	Hamstrings and all muscles below knee	Tibial and common peroneal territories (latter more common if partial)
Yoga paralysis	Sciatic notch	May also involve superior/inferior gluteal nerve	? + posterior cutaneous nerve of thigh
Catamenial sciatica (with endometriosis)			
Peroneal nerve			
Strawberry picker's, (olive) harvester's, turnip picker's or hoeing palsy	Popliteal fossa, lateral fibular head and fibular tunnel	Tibialis anterior, extensor hallucis longus, extensor digitorum and peronei	Lateral lower leg and dorsum of foot
Anterior (tibial) compartment syndrome	Tibial compartment	Tibialis anterior, extensor hallucis longus, extensor digitorum	Interspace and dorsum of digit I and II
Anterior tarsal tunnel syndrome	Ankle	None	Interspace and dorsum of digit I and II

Continued on p. 374

Table 9.14 *Continued*

Colloquial terminology	Sites of compression	Weakness	Sensory loss
Tibial nerve			
Tibial neuropathy	Posterior knee	Gastrocnemius, soleus, tibialis posterior, flexor digitorum longus and intrinsic foot muscles	Sole of foot +/– sural
(Posterior) tarsal tunnel syndrome	Tarsal tunnel	Intrinsic foot muscles	
Femoral nerve	Pelvis, thigh	Psoas, quadriceps	Anterior thigh and medial aspect of calf
Lateral cutaneous nerve of the thigh			
Meralgia paraesthetica	Inguinal ligament	None	Lateral thigh

Table 9.15 Causes of median neuropathy at the elbow.

- Fractured humerus
- Elbow dislocation
- Direct trauma
- Anatomical compression
  - Supracondylar ligament/spur
  - Biceps aponeurosis
  - Pronator teres
- Tumours and masses
- Angiography/venepuncture

radial, long thoracic, 'tarsal tunnel' (distal tibial [posterior] and peroneal [anterior] neuropathies) and femoral neuropathies.

History, examination and investigation follow similar principles to those outlined above. These are outlined with their colloquial terminology in Table 9.14. For more detailed descriptions the reader is referred to Stewart (2000).

Median nerve compression and carpal tunnel syndrome

Median nerve compression between the flexor retinaculum of the wrist and the bones of the carpus is referred to as carpal tunnel syndrome (CTS) and is the most common of the median compression palsies. The prevalence has been estimated at more than 6% of the population.

Compression in the more proximal upper limb occurs more rarely. Median nerve compression in the axilla usually co-occurs with radial and ulnar nerve involvement and is most commonly caused by traumatic or surgical injury, or unusual compressive forces (e.g. crutches or heavy sleep through intoxication). In the upper arm trauma is the most common insult and the median nerve may be affected in isolation. At the elbow the median nerve is susceptible to numerous injuries (Table 9.15). Compression at the elbow or more proximally leads to inability to pronate the forearm and flex the distal phalanx of thumb and index finger (orator's hand). Numbness affects the palm as well as the distal fingers.

Carpal tunnel syndrome

Carpal tunnel syndrome is three to eight times more common in women than men. It most commonly affects both hands, usually the dominant hand first. There are many recognized causes of CTS (Table 9.16). Numbness, paraesthesiae and pain in the hand and sometimes in the more proximal arm, often occurring at night, are the most common presenting complaints. When the pain is intermittent, shaking the hand or wrist relieves the symptoms and is a relatively reliable sign of compression at the wrist (more reliable than Phalen's, Tinel's or other provocative signs). If not treated, sensory symptoms become permanent and weakness and wasting of the thenar eminence may become apparent.

Examination

Compression of the median nerve at the wrist typically results in weakness of abductor pollicis brevis, opponens pollicis, first and second lumbricals and sometimes flexor pollicis brevis and sensory disturbance on the palmar skin of the thumb, second, third and half the fourth digit. There are many anatomical variations. The palmar cutaneous branch arises proximal to the flexor retinaculum and does not pass through the carpal tunnel. Occasionally, the motor branch may pierce the retinaculum and may escape compression but be damaged during surgery.

Investigation

Nerve conduction studies are required to confirm the diagnosis as demonstration of the clinical symptoms and signs is not 100% reliable. About 5% of studies are thought to be falsely negative, but a negative study should provoke a search for an alternative diagnosis (C6/7 radiculopathy, thoracic outlet syndrome or thalamic infarction). Where anatomical variants or structural

Table 9.16 Causes of carpal tunnel syndrome.

- Rheumatoid arthritis
- Bony osteophytes, degenerative wrist disease, wrist fractures
- Gouty tophi
- Congenitally narrow tunnel
- Intracanalicular ganglia
- Work-related repetitive strain
- Pregnancy
- Hypothyroidism/hyperthyroidism
- Diabetes
- Acromegaly
- Amyloidosis
- Vasculitides
- Multiple myeloma
- Chronic renal failure, uraemia and dialysis
- Mucopolysaccharidosis
- Infections
- Predisposing conditions
  - Diabetes
  - Hereditary neuropathy with liability to pressure palsies
  - Inflammatory neuropathies (e.g. CIDP, MMNCB)
- Idiopathic

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; MMNCB, multi-focal motor neuropathy with conduction block.

abnormalities of the wrist are considered MRI can be most helpful in assisting both diagnostician and surgeon. The yield from haematological and biochemical testing where no pathology is detected on thorough clinical examination is low.

Treatment

There is evidence of variable quality that non-surgical interventions including oral steroids, ultrasound, yoga and carpal bone mobilization are effective in the short term for symptom relief. There is no benefit from the use of non-steroidal anti-inflammatory drugs or diuretics. Local steroid injections may provide short-term relief. Surgical decompression gives the most satisfactory clinical relief (90–95% success) in both the short and long term (3% recurrence rate) and is associated with minimal risks. Results are better if symptoms have been present for less than 3 years. Endoscopic release has few advantages over open procedures and is more often associated with failure.

Ulnar nerve compression

The ulnar nerve can also be damaged anywhere along its course from the brachial plexus to the hand. The most common site of damage is at the elbow. Here the nerve is exposed to trauma, pressure and stretching as it passes the medial epicondyle through the ulnar groove and then deep to the flexor aponeurosis under flexor carpi ulnaris. Other causes reflect the causes of median neuropathy (Table 9.17). An extensive differential diagnosis of conditions mimicking ulnar neuropathy exists (Table 9.18).

Table 9.17 Causes of ulnar neuropathy.

- Bony deformity at elbow
  - Fractures
  - Rheumatoid arthritis
  - Osteophytes
  - Paget's disease
  - Congenitally shallow condylar canal
- Pressure
  - Bony
  - Prolonged elbow flexion
  - Peri-operative/ITU compression
  - Soft tissue/neural/bony masses
  - Variable anatomy (muscles/fibrous bands)
  - Supracondylar spur
- Diabetes
- Vasculitides
- Leprosy
- Predisposing conditions
  - Diabetes
  - Hereditary neuropathy with liability to pressure palsies
  - Inflammatory neuropathies (e.g. CIDP, MMNCB)
- Idiopathic

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; MMNCB, multi-focal motor neuropathy with conduction block.

Table 9.18 Conditions mimicking ulnar neuropathy.

- Cord lesions/myeloradiculopathy
- Syringomyelia
- Hirayama monomelic atrophy
- Amyotrophic lateral sclerosis
- C8/T1 radiculopathy
- Thoracic outlet syndrome
- Lower brachial plexus lesions (trauma/infiltration/radiation/post sternotomy)
- Brachial neuritis (neuralgic amyotrophy)
- Multi-focal motor neuropathy with conduction block

Symptoms

Numbness and tingling affecting the fourth and fifth digits of the hand are the most frequent presenting complaints. Deep pain may be felt proximal to the nerve. Weakness of hand grip appears later but may be the only symptom in some. The elbow may be identified as a site of previous damage, trauma or pressure and occasionally sensitivity of the ulnar nerve at the elbow is reported.

Signs

Accurate clinical localization of ulnar neuropathies is essential to guide exploration and treatment. Weakness of first dorsal interosseous and abductor digiti minimi in the hand is most common. Motor branches and the distal superficial cutaneous branches all pass through Guyon's canal; signs confined only to this territory could result from compression at the wrist or more proximally. Sensory loss should not extend above the wrist; the medial cutaneous nerve of the forearm emerges from the brachial plexus. Weakness of the flexor digitorum profundus to the fourth and fifth digits or flexor carpi ulnaris puts the lesion at the elbow or above. Involvement of the palmar skin of the medial border of the hand or the dorsal skin of the affected fingers excludes compression in Guyon's canal at the wrist. Additional weakness of median nerve innervated muscles (see above) suggests alternative diagnoses. The presence of a thickened nerve at the elbow suggests inflammatory, hereditary, tumourous or lepromatous involvement.

Treatment

Effective treatment of ulnar neuropathies usually involves surgical intervention. Conservative measures aimed at educating the patient to avoid leaning on the elbow, nocturnal splinting and diffusing pressure with sheepskin elbow pads may all assist. Surgery should be offered to all patients who have sensory and motor signs consistent with the diagnosis, especially if there is clear worsening. Patients with sensory signs only should be closely reviewed to detect signs of progression – most will remit. In late severe cases with weakness, wasting and sensory loss surgical intervention may not be beneficial but tendon transfer procedures may help hand function. Surgical approaches involve removing compressing structures (e.g. masses) if appropriate, and thereafter releasing and mobilizing the nerve to a greater or lesser extent. Transposition of the nerve is associated with greater risks of peri-operative damage and thus extensive exploration and release may often be the most appropriate intervention.

Other ulnar neuropathies

Ulnar neuropathies at other sites are identified by careful history-taking, examination directed at ulnar nerve innervation and more widely in the neck, chest and upper limb and neurophysiological 'inching studies' (inch by inch). Imaging (both MR and ultrasound) will be more widely used to identify abnormalities in other sites than the elbow.

Common peroneal neuropathies

Isolated lesions of the peroneal nerve are the third most common of the mononeuropathies. The common peroneal nerve is most liable to damage as it winds laterally around the knee and fibula head. It then passes through the fibular tunnel (a fibrous arch derived from peroneus longus) before dividing into superficial and deep peroneal nerves (Figure 9.7).

Symptoms

Complete common peroneal lesions cause a foot drop with inability to evert the foot or extend the toes and a characteristic high-stepping and audibly slapping gait. The sensory loss covers the lower half of the lateral part of the leg and dorsum of the foot, sparing the sural nerve territory. The history may or may not reveal an obvious cause (Table 9.19). A history of focal pain elsewhere in the leg or other systemic symptoms should prompt a search for a local or systemic cause.

Table 9.19 Causes of common peroneal nerve palsy.

- Pressure
  - Leg crossing
  - Prolonged crouching (e.g. childbirth, 'strawberry pickers' palsy, yoga)
  - Lithotomy stirrups
  - Plaster casts
  - Peri-operative/ITU
  - Anterior (fibial) compartment syndrome
- Nerve entrapment
  - Fibula tunnel
  - Post fracture fibrosis
- Trauma
  - Direct penetrating or blunt trauma
  - Fibula fracture
  - Knee dislocation
- Popliteal fossa lesions
  - Baker's cyst, haematoma, DVT
- Nerve tumours
  - Neuroma, schwannoma, lymphoma
- Diabetes
- Leprosy
- Vasculitis
- Idiopathic

DVT, deep venous thrombosis.

Signs

The site of the lesion may be clear from the history or obvious site of damage from examination. However, the variability of innervations in the leg, and common occurrence of partial nerve lesions of the sciatic, lumbo-sacral trunk or multiple radiculopathies, means that an electrical study is often crucial for localizing the site of damage and directing further investigation and treatment.

Investigation

Nerve conduction and EMG studies enable localization of any lesion from root (often L5) through the lumbosacral trunk and sciatic nerve to the more distal branches of the superficial and deep peroneal nerves. Although plain radiographs, CT and arteriography have diagnostic use in specific scenarios, MRI scanning has greatest utility in demonstrating intrinsic and extrinsic mass lesions (both tumours and inflammatory) of the nerve.

Treatment

Acute trauma with nerve transection or compartment syndromes are surgical emergencies and intervention to explore and relieve pressure and/or repair the nerve is indicated. Where an identified episode of prolonged nerve compression is identified avoidance of further injury and watchful waiting are appropriate. Most lesions recover. Lesions that progress or fail to recover, or lesions associated with other structural abnormalities should be surgically explored.

Plexopathies

The two major nerve plexuses are the brachial and lumbosacral. Lesions of a plexus cause complex post-ganglionic motor and sensory deficits in the distribution of part or all of the plexus. The reader is referred to the anatomical diagrams (Figures 9.3 and 9.6) to assist with identifying and localizing involvement. Causes are shown in Table 9.20. Many of these are common to both plexuses. Some, e.g. neuralgic (brachial) amyotrophy and diabetic lumbosacral plexopathy have a predilection for one or the other.

Table 9.20 Plexopathies (brachial or lumbosacral, except where indicated).

Trauma (mostly brachial plexus)
Shoulder injury – upward or downward
Peri-operative
  Arm manoeuvres during pharmacological neuromuscular paralysis
  Median sternotomy
  Jugular/subclavian cannulation and thrombosis
  Shoulder supports in head-down procedures
Fracture dislocation
Traction in newborns (Klumpke palsy)

Compression
Back pack
Haematomas and aneurysms
Thoracic outlet syndrome
Pregnancy and prolonged labour (lumbosacral plexus)
Retroperitoneal masses (lumbosacral plexus)
  Abscess
  Haematoma
Abdominal aortic aneurysms (lumbosacral plexus)

Malignancy
Invasive e.g. metastases
  Brachial – lung (Pancoast), breast, lymphoma, melanoma
  Lumbosacral – cervix, ovary, colon, prostate, bladder
Primary – neurofibroma and malignant nerve sheath tumour
Radiotherapy

Acute brachial neuritis (e.g. neuralgic amyotrophy/Parsonage–Turner syndrome/acute brachial plexus neuropathy)

Diabetes (most commonly lumbosacral plexopathy)

Vasculitis

Inflammatory
  CIDP
  MMNCB

Hereditary
  Hereditary brachial plexopathy (Septin)
  Hereditary neuropathy with liability to pressure palsies (chromosome 17p11.2 deletion)

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; MMNCB, multi-focal motor neuropathy with conduction block.

Acute brachial neuritis

Parsonage and Turner described this entity also known as neuralgic amyotrophy in 1948. Typically, acute deep aching pain occurs spontaneously and affects the neck, shoulder and upper arm in a diffuse pattern. This may last from hours to 2 weeks or more and is followed by focal wasting and weakness, most commonly in the distribution of nerves originating from the upper plexus (deltoid, serratus anterior, supraspinatus and infraspinatus and biceps). Muscles in the distributions of the lower plexus may also less commonly be affected. Sensory symptoms occur in about one-third of patients and signs in about two-thirds, most often sensory loss in the territory of the axillary nerve. Prolonged pain, bilateral involvement, structural or mass lesions on examination should prompt a search for an alternative cause.

The cause of brachial neuritis remains uncertain. Occasional rapid recovery and the finding of conduction block point to demyelination as an initial mechanism but clearly axonal degeneration swiftly follows. Rare pathological reports of inflammatory nerve lesions exist. Associations with immunizations, infections, trauma, surgery, pregnancy and childbirth, intravenous heroin and vasculitides point to an immune mechanism. Steroids, although sometimes useful for pain, usually fail to alter the outcome. Other analgesics (including opioids) are usually necessary. About 90% of patients with a typical brachial neuritis will recover in 3 years. Raraly, a similar condition affects the lumbosacral plexus.

Anterior horn cell diseases

Many motor nerve diseases principally affect the anterior horn cell body; these are usually neurodegenerative (e.g. motor neurone disease) or hereditary (e.g. spinal muscular atrophy). However, there is a broad differential diagnosis (Table 9.21).

Motor neurone disease

Motor neurone disease (MND) is a progressive neuronal degenerative disease that leads to severe disability and death. There is considerable variability in presentation, clinical course and prognosis. The condition is divided into several different clinical subtypes. Amyotrophic lateral sclerosis (ALS) is the most common and is characterized by upper and lower motor neurone involvement of the bulbar, upper and lower limb territories; presentation with predominantly or exclusive bulbar weakness is referred to as progressive bulbar palsy (PBP). In primary lateral sclerosis (PLS) there is exclusively upper motor neurone involvement and progressive muscular atrophy (PMA) involves only lower motor neurones.

Amyotrophic lateral sclerosis

The onset of ALS is usually with focal wasting and weakness affecting contiguous limb muscles more commonly in the upper limbs. Occasionally, there may be severe isolated wasting and weakness of individual limbs (e.g. flail arms). Other patients may present

Table 9.21 Differential diagnosis of motor neurone disease.

Bulbar weakness
Myasthenia gravis
Oculopharyngeal dystrophy
Brainstem lesion (tumour, infarction, infection, demyelination)

Upper motor neurone
Cervical spondylosis/radiculopathy
Familial spastic paraparesis
HTLV1-related myelopathy
Subacute combined degeneration
Adrenoleucodystrophy
Multiple sclerosis

Lower motor neurone
Spinal muscular atrophy
X-linked bulbospinal neuronopathy (Kennedy's disease)
Distal hereditary motor neuropathies
Postpolio syndrome
CIDP
Multifocal motor neuropathy with conduction block
Charcot–Marie–Tooth diseases
Benign monomelic amyotrophy
Hexosaminidase A deficiency
Polymyositis
Inclusion body myositis
Multiple radiculopathies

Other
Thyrotoxicosis
Lead, thallium, arsenic toxicity
Konzo
Radiation
Auto-immune disorders
Syphilitic pachymeningitis
Paraneoplastic syndromes

with progressive dysarthria. Rarely, there may be selective involvement of respiratory muscles leading to respiratory failure.

ALS is characterized by the progressive development of wasting, fasciculations, cramps, weakness, spasticity, brisk reflexes and extensor plantar responses. Limb involvement is more often distal than proximal and leads to weakness of the hands or bilateral foot drop. Patients may complain of clumsiness or impaired mobility. Bulbar involvement is characterized by dysarthria, tongue wasting, fasciculations, slow movement, brisk jaw jerk, sialorrhoea and dysphagia. Patients complain of difficulty speaking or occasionally hoarseness which usually precedes swallowing difficulties. Clear fluids tend to aspirate causing the patient to cough after drinking. Hypersalivation becomes difficult to clear and leads to the development of drooling and dribbling. Pseudobulbar involvement is also associated with pathological emotional lability in which there is excessive uncontrolled laughter or crying.

Fasciculation is variable but may be prominent after exercise. It is well seen in the tongue and across the back. Head droop may be an early feature because of weakness of the neck extensors and paraspinal muscles. Progressive respiratory muscle weakness may lead to exertional dyspnoea but selective diaphragm weakness will cause breathlessness on lying flat and progressive hypoventilation. Increasing limb and truncal weakness causes worsening immobility and self-care. Bulbar weakness leads to increasing difficulty with communication and eventual anarthria with worsening dysphagia. Sleep disturbance is common and multi-factorial related to difficulty turning in bed, periodic limb movements, hypersalivation and inability to clear secretions, difficulty with communication, emotional lability and depression. Sensory, ocular and bladder symptoms are unusual.

Progressive bulbar palsy

PBP is restricted to bulbar musculature at presentation and during the initial progression. Subsequent spread to the cervical regions and then more generally is common after months. PBP constitutes about 15–20% of cases of MND and is associated with a poor prognosis with a median survival of 2 years.

Flail arm/leg syndrome

Progressive isolated wasting and flaccid weakness of an arm or leg may be the presenting feature in up to 10%. Upper motor neurone features develop later. This form of the condition is considerably more common in males and carries a better prognosis than ALS, with median survival of 57 months.

Primary lateral sclerosis

This is an exclusively upper motor neurone form of MND which occurs in about 5% of patients. Lower motor neurone features may develop in a minority after 5–10 years. The condition develops at an older age and may be slow in its progression. A survival of 20 years is relatively common. Bladder symptoms are common but bulbar involvement occurs later and is less severe.

The hemiplegic variant of Mills is a rare presentation with mixed upper and lower motor neurone signs occurring on one side of the body.

Aetiology

MND can be associated with genetic or acquired factors or may occur sporadically (Table 9.22).

Genetics

Between 5% and 10% of cases of ALS are familial (FALS) and most have an AD pattern of inheritance. In approximately 20% of patients with FALS the genetic defect is a mutation on chromosome 21 in the gene for copper/zinc superoxide dismutase (*SOD1*). More than 100 mutations of the *SOD1* gene are now known. There is a small incidence of *SOD1* mutation occurring in sporadic MND. *SOD1* mutation screening is available, but counselling is important before predictive testing can be

Table 9.22 Forms of motor neurone disease.

Genetic
Familial ALS
Brown–Vialetto–van Laere syndrome
Fazio–Londe
Hexosaminidase A deficiency
HSP
SMA
X-linked bulbo-spinal atrophy (Kennedy's disease)
Multisystem (spino-cerebellar)

Sporadic
Sporadic MND (PBP, ALS, PMA)
PLS
Distal focal SMA (Hirayama)
Madras form
Western Pacific form
MND and fronto-temporal dementia
Multi-system atrophy
Progressive supranuclear palsy
Cortico-basal degeneration

Acquired
HTLV1-associated myelopathy
HIV-associated MND
Creutzfeldt–Jakob disease
Acute poliomyelitis and post polio syndrome

ALS, amyotrophic lateral sclerosis; HSP, hereditary spastic paraparesis ; HTLV, human T-lymphocyte virus; MND, motor neurone disease; PBP, progressive bulbar palsy; PLS, primary lateral sclerosis; PMA, progressive muscular atrophy; SMA, spinal muscular atrophy.

undertaken and genetic screening for predictive testing is not performed routinely. Mutations in several other chromosomal loci have now been described in patients with autosomal recessive inheritance.

Environmental

There is a 50–150 fold increase in the incidence of MND in the Western Pacific. The condition differs pathologically from sporadic ALS because dementia and parkinsonism frequently coexist. Furthermore, unlike sporadic ALS, the pathological findings are characterized by the presence of neurofibrillary tangles. It seems likely this form of the condition is related to a toxin, possibly from the cycad seed.

Lymphoproliferative disease

An association between MND and lymphoproliferative disorders has been reported. PLS may rarely occur as a paraneoplastic disease associated with antineuronal antibodies.

Diagnosis of MND

Routine haematology and biochemical screening is usually normal. Creatine kinase (CK) may be mildly or moderately elevated. Underlying lymphoproliferative, infective, endocrine or toxic causes should be excluded. Hexosaminidase A should be checked in the young and ANA in late presentation. Genetic analysis may include *SOD1* and *SMN* in the predominantly lower motor neurone presentation.

Investigation

Neurophysiology is essential in establishing the diagnosis and severity of MND and excluding the differential diagnoses (Tables 9.21 and 9.22). Sensory nerve action potentials (SNAPs) are normal and motor conduction velocities should be >70% of normal. There must be no conduction block. Needle EMG shows neurogenic changes of denervation and reinnervation. There is considerable variability in EMG findings and extensive sampling of bulbar, cervical, thoracic and lumbosacral muscles may be necessary. MRI is important to exclude structural or inflammatory conditions which may mimic MND. MR imaging may show high signal in the descending pyramidal tracts indicating Wallerian degeneration. Positron emission tomography (PET) imaging has shown cortical changes, particularly in patients with cognitive impairment.

Incidence and prognosis

The annual incidence is 1.5–2/100,000 and the prevalence approximately 4–8/100,000. Males are more commonly affected than females (1.5 : 1). The incidence increases with age with a mean age of onset of 63 years.

The natural history of MND is variable and occasional prolonged periods of stability may occur. Patients with PBP have the worst prognosis because of the risk of aspiration with a median survival of 2–2.5 years. In ALS the mean disease duration is 3–4 years. Over 50% of patients die within 3 years and 90% within 5 years of the first symptom. In PLS a survival of 20 years is relatively common. In general, rapid rate of progression, early respiratory or bulbar symptoms and increasing age are adverse prognostic indicators, while exclusively upper or lower motor neurone syndromes and young age are associated with a better prognosis.

Management

Telling the patient the diagnosis

The communication of the diagnosis is a major and potentially devastating life event which must be handled with great sensitivity. All too often patients complain that the diagnosis has been given in a hurried, off-handed and inappropriate manner. The diagnosis should be explained by a senior physician, in a quiet and private room, with a carer present. The consultation should be sensitive. The patient should be provided written comprehensible information, and a follow-up appointment within a few weeks. Ongoing follow-up should be supervised by a single named doctor, in close liaison with the GP and community services. The diagnosis and details of the information given to the patient and the management plan must be communicated to the GP without delay.

Table 9.23 Important websites related to motor neurone disease.

www.wfnals.org	World Federation of Neurology, Amyotrophic Lateral Sclerosis site
www.mndassociation.org	Motor Neurone Disease Association (England, Wales and Northern Ireland)
www.alsmndalliance.org	International Alliance of ALS/MND Associations
www.cochrane.org	The Cochrane collaboration (includes report on riluzole)
www.theabn.org/downloads/mnddoc.pdp	Guidelines for the management of motor neurone disease, endorsed by the Association of British Neurologists
www.alsa.org	ALS Association (USA)
www.scotmnd.org.uk	Scottish Motor Neurone Disease Association
www.nice.org.uk	National Institute for Clinical Excellence – includes review and recommendations for the use of riluzole

Principles of management

The management of MND involves the coordination of multidisciplinary care with a team that will include the patient's own GP and primary care team, occupational and physiotherapists, clinical nurse specialists, support and social workers and the palliative care team. The supervising neurologist or physician should coordinate a continuum of care for each patient from diagnosis to the terminal phase of the disease. Each member of the team will have an individual role. In the UK *The Motor Neurone Disease Association (MNDA)* employs a network of Regional Care Advisors (RCA). These individuals act as a point of contact for people with MND and their carers, and help to point to the provision of pieces of equipment such as splints, communication aids, which may be needed. They also provide a telephone helpline and are able to contribute to the support of relatives and carers following the death of the patient. Important websites are listed in Table 9.23.

Pharmacotherapy

Riluzole inhibits glutamate release and is the only drug which has been shown to increase survival in MND. Riluzole prolonged survival by 3 months after 18 months administration with little or no effect on functional deterioration in two clinical trials. It is usually well tolerated with occasional nausea and fatigue. The drug should be discontinued if liver function tests exceed five times the upper limit of normal. Many patients look to other possible treatments and antioxidants (vitamins C and E) and creatine are in common use. Acupuncture, reflexology, chiropractic and massage may contribute to the individual's personal feeling of well-being.

Respiratory management

Respiratory impairment is common and may develop because of respiratory muscle weakness, impaired bulbar function and obstructive sleep apnoea (OSA) or defects in central control. It should be anticipated in all patients with a diagnosis of MND. Dyspnoea may be caused by infection, pulmonary embolus or airway obstruction from mucus plug or inhaled pharyngeal contents. Prompt use of antibiotics should be supplemented with physiotherapy. Annual influenza vaccination should be undertaken. Nocturnal hypoventilation and OSA present as daytime hypersomnolence, lethargy, morning headaches, poor concentration, depression, anxiety and irritability with or without snoring and restless sleep with abnormal movements.

FVC reflects respiratory muscle strength, and serial measurements may be useful in predicting the onset of respiratory failure and non-invasive ventilation is often initiated when FVC is <50% of predicted. Other markers of impending respiratory failure include maximal inspiratory and expiratory mouth pressures and maximum sniff nasal pressure. Polysomnography, diaphragmatic EMG and phrenic nerve conduction studies may provide useful additional information.

Respiratory support can provide symptomatic relief and increase life expectancy. These benefits must be balanced against the demands on carers, practical problems of administration, the risk of iatrogenic problems, and distressing and unwanted prolongation of life in the terminal stages of MND. Many of these difficulties can be avoided by early and careful discussion with patients and their carers. Elective ventilatory support is usually administered non-invasively (NIV), initially during sleep. NIV allows speech, oral feeding and leads to fewer respiratory infections. However, it may not be desirable in patients with severe bulbar weakness, facial abnormalities or where aspiration has already occurred. Some patients require ventilatory support for increasing periods and may choose to undergo tracheostomy. Tracheostomy carries a significant risk of complications and considerable difficulties in domiciliary management. There remains a concern that tracheostomy may lead to prolonged survival in the face of severe disability. Many patients will decide to use NIV support if their respiratory function deteriorates and is symptomatic. The provision and supervision of respiratory support should be through a specialist MND centre.

Management of bulbar weakness

Bulbar palsy is one of the most distressing features of MND. Weakness of tongue, pharynx and facial muscles results in slow eating, choking, drooling, dysarthria and dysphonia. Sialorrhoea is generally managed with anticholinergic agents including atropine or amitriptyline taken orally, hyoscine (scopolamine) transdermally or glycopyrronium bromide subcutaneously. Side effects are common in the elderly. Antimuscarinic agents render secretions viscid whereas β-blockers have been reported to reduce secretions without increasing tenacity. A portable home suction device and cough enhancement techniques may be helpful. Unilateral parotid gland irradiation and parotid botulinum toxin injection have also been used.

Dysphagia

The management involves speech and language therapy assessment of swallow and advice on techniques to ease mastication and prevent aspiration.

Nutrition

Patients with dysphagia may have inadequate calorific and fluid intake, leading to accelerated weight loss and dehydration. The initial management of dysphagia in ALS includes modification of food and fluid consistencies while ensuring maximal calorific intake. Percutaneous endoscopic gastrostomy (PEG) should be considered as an alternative or supplementary route for nutrition, hydration and medication. PEG should be undertaken before FVC falls below 50% of predicted as it is more successful, improves survival and is less complicated at this early stage. Radiologically inserted gastrostomy (RIG) tubes do not require sedation or endoscopy and are preferable in patients with respiratory compromise.

Communication

Progressive dysarthria is common and speech may become severely impaired or lost within a short time. Simple techniques for improving the intelligibility of speech include reducing background noise and facing the speaker. Writing is often an excellent alternative to speech if limb function is preserved. There are a variety of other aids ranging from pointing boards to computerized speech synthesizers.

Limb dysfunction

Musculoskeletal pain is common and may respond to antispasticity agents, NSAIDs and stronger analgesics including opiates. Skin pressure pain caused by immobility may also occur. Cramps are usually nocturnal and may respond to quinine sulphate, diazepam, carbamazepine or phenytoin. Stiffness may be caused by spasticity or muscle or joint contracture. Tizanidine and baclofen may help with the pain of spasticity.

Cognitive impairment in ALS

MND is associated with both mild frontal lobe impairment and also a more severe form of fronto-temporal dementia. Cognitive impairment occurs most often in patients with PBP who may show changes in character, personality and behaviour. However, this is difficult to assess because of the speech disturbance, motor retardation associated with pseudobulbar palsy and the obvious distress, anxiety and frequently depression. Fronto-temporal dementia is characterized by disinhibition, loss of insight and social awareness, impulsivity, reduced speech output with echolalia and eventual mutism. In the late stages there may also be anxiety, agitation, apathy and even delusions. There are characteristic pathological changes including frontal temporal neuronal loss, gliosis and spongiform change.

Psychological factors

Depression and anxiety often follow the diagnosis of MND. The drugs of choice are SSRIs. Anxiety may require specific drug therapy. This may be short-term treatment with benzodiazepines or amitriptyline. If aggression and disinhibition occur with cognitive impairment, phenothiazines may be necessary and psychiatric support is often helpful. Emotional lability may be distressing for patient and carers and may be eased by amitriptyline or an SSRI.

Other symptoms

Insomnia is common in MND. If sleep remains disturbed after relief of pain then amitriptyline is preferable to hypnotics for sedation. Constipation is treated by dietary modification, ample fluid intake and aperients.

With severe pyramidal involvement bladder frequency and urgency may occur requiring oxybutinin.

Terminal care

Palliative care should be introduced before the terminal stages of MND. Home care teams and day centres may offer respite care in parallel with home carers. Close liaison between GP, community health care and hospice teams and palliative care physicians is essential.

Terminal care often involves alleviating psychological distress and the symptoms of bulbar weakness and respiratory failure. Patients may experience a frightening sensation of choking because of episodes of laryngospasm. Benzodiazepines and agents to dry secretions may be helpful but laryngospasm usually resolves spontaneously. Oral, subcutaneous or intravenous morphine may be indicated to relieve dyspnoea, anxiety, pain or other distress. The effectiveness of sedatives such as diazepam, midazolam or chlorpromazine in reducing anxiety in the terminal stages outweighs any depressive action of the drugs on respiratory function.

The ‘Breathing Space Kit’, provided by the Motor Neurone Disease Association in the UK, contains medication which can be used by the carer, nurse or GP for the emergency treatment of acute episode of respiratory distress which often occurs in the terminal stages. These include diazepam, diamorphine, chlorpromazine and hyoscine.

Carers

Following the death of an MND patient the family and carers will require bereavement support. This may be provided by the palliative care team but continuing domiciliary support may also be necessary.

Spinal muscular atrophy

Spinal muscular atrophy (SMA) represents a group of predominantly autosomal recessive disorders characterized by degeneration of anterior horn cells and bulbar nuclei. After cystic fibrosis, SMA is the second most common autosomal recessive disease of childhood (1/6000–10,000 live births). There are four clinically distinct types (Table 9.24).

1. *SMA Type I:* infantile SMA (Werdnig–Hoffmann disease);
2. *SMA Type II:* intermediate SMA;
3. *SMA Type III:* juvenile SMA (Kugelberg–Welander disease);
4. *SMA Type IV:* adult onset SMA.

Table 9.24 Summary of spinal muscular atrophy (SMA).

Condition	Genetic association	Clinical features
SMA Type I (infantile, Werdnig–Hoffman)	5q13 (SMN gene)	see text
SMA Type II (intermediate)	5q13 (SMN gene)	
SMA Type III (juvenile, Kugelberg–Welander)	5q13 (SMN gene)	
SMA Type IV Adult onset	Variable (AR or AD)	
X-linked arthrogryposis multiplex (X-linked infantile SMA)	Xp11.3–q11.2	Hypotonia, areflexia, multiple congenital contractures. Death in infancy
Diaphragmatic SMA (HMN III, IV)	11q13	Distal limb weakness
SMARD (HMN VI)	1GHMB2	Diaphragm weakness, death in infancy
Distal SMA (HMN V)	7p15 (GARS)	Often sporadic, predominantly upper limb

GARS, glycyl-tRNA synthetase; HMN, hereditary motor neuropathy; SMARD, SMA with respiratory distress type 1; SMNgene, survival motor neurone gene.

There are also rarer variants affecting bulbar, limb girdle, musculature and diaphragm with various patterns of inheritance (nomenclature tends to vary).

Genetics and aetiology

The most common types of SMA are associated with defects in ribonucleic acid (RNA) processing. Spinal muscular atrophy types I–III and some of type IV (95% of the total SMA cases) are associated with reductions in the product of the survival motor neurone (*SMNI*) gene (chromosome 5q11.2–5q13.3). The *SMNI* gene encodes a protein involved in RNA metabolism and the severity of the phenotype correlates with the level of SMNI protein. In the majority of patients it is functionally absent and survival depends on the expression of the *SMNII* gene.

Clinical features

SMA Type I (infantile, Werdnig–Hoffmann)

This develops in infancy with failure to achieve a sitting posture and death by 2 years. There may be loss of fetal movements *in utero* and the baby is born floppy with a weak cry and failure to suck, swallow and achieve head control or sitting posture. Contractures develop after immobilization and death usually occurs by 2 years as a result of respiratory failure.

SMA Type II (intermediate)

In SMA Type II (intermediate SMA) muscle weakness develops after 6 months and manifests as motor development delay. Independent sitting is achieved but not walking. Kyphoscoliosis, severe contractures, skeletal deformity and respiratory muscle weakness may lead to death in early adulthood but prolonged survival is possible if respiratory involvement is limited or with appropriate ventilatory support.

SMA Type III (juvenile, Kugelberg–Welander)

SMA Type III (juvenile SMA) becomes symptomatic in early childhood (>18 months) and patients achieve mobility. Fasciculation, cramps and a fine tremor are common and there is proximal limb weakness and wasting more prominent in the lower limbs. SMA III is highly variable and often stabilizes. Prognosis can often be predicted by the age of onset and severity. SMA III may be compatible with normal life expectancy.

Table 9.25 The differential diagnosis of spinal muscular atrophy (SMA).

- Limb girdle muscular dystrophy, dystrophinopathy (Duchenne and Becker)
- Acid maltase deficiency
- Hexosaminidase deficiency
- Congenital myopathy – nemaline, central core
- Myasthenia gravis, polymyositis
- CIDP
- CMT 2
- Kennedy's disease
- MND
- Paraneoplastic syndromes

SMA Type IV (adult onset)

Adult SMA represents a heterogeneous group. An autosomal dominant pattern of inheritance accounts for up to 30% of cases and is not associated with chromosome 5 abnormalities or known dHMN mutations. The clinical pattern is variable with onset between the third and sixth decades. There may be slowly progressive limb girdle or scapulo-peroneal weakness with difficulty climbing stairs, arising from chairs or walking that resembles limb girdle dystrophy. Respiratory muscle involvement and scoliosis are rare but there may be vocal cord impairment.

Other forms of SMA

Severe forms of SMA associated with death in infancy include X-linked arthrogryphosis multiplex (X-linked infantile SMA) characterized by hypotonia, areflexia and multiple congenital contractures and diaphragmatic SMA (SMARD-1) in which there is gynaecomastia, congenital fractures and sensory neuropathy (see below). Fazio–Londe is a form of MND limited to the lower cranial nerves starting in the second decade of life and progressing to death over 1–5 years. Brown–Vialetto Van Laere presents largely in females in the second decade with bulbar palsy and deafness.

Distal SMA is a misnomer and is covered under distal hereditary motor neuropathies. Differential diagnosis: see Table 9.25

Kennedy's disease (X-linked bulbo-spinal neuronopathy)

Kennedy's disease is of particular importance because the clinical pattern resembles MND. With a frequency of 1/50,000 it is not uncommon. Kennedy's affects males with onset in the third decade or later. It is caused by a CAG trinucleotide repeat expansion in the androgen receptor gene. The condition is characterized by prominent oral and perioral fasciculation, muscle cramps, progressive dysarthria and dysphagia and progressive lower motor neurone bulbar, shoulder girdle, axial and limb weakness. UMN signs are not seen. Sensory involvement occurs. Associations include gynaecomastia, diabetes mellitus, testicular atrophy and infertility. Kennedy disease progresses more slowly than conventional MND and respiratory muscle involvement is less common. Serum CK may be elevated and nerve conduction studies may show reduced amplitude of both motor and sensory action potentials with diffuse, predominantly chronic denervation changes on EMG. The diagnosis is confirmed by genotyping.

Hexosaminidase-A deficiency

The most severe form of hexosaminidase-A deficiency is Tay–Sachs syndrome (Chapter 18). However, a milder form may develop in children or adults characterized by a form of SMA associated with prominent muscle cramps, tremor, dementia, cerebellar atrophy and sensory involvement.

Investigation

Serum CK is often normal in SMA I–IV but elevated in Kennedy, SMARD-1 and other rare forms of SMA.

Neurophysiological studies show reduced CMAPs but normal conduction velocities and SAPs, except in Kennedy's where sensory involvement is identified in 80% of cases. EMG shows acute denervation and chronic reinnervation. Muscle biopsy is not especially helpful and shows features of acute denervation and secondary myopathic change.

Genetic confirmation of mutations in the *SMN1* or androgen receptor genes is diagnostic. Mutations may not be found in some rare forms of childhood SMA and in many patients with adult onset SMA.

Management

There is no specific treatment available for SMA. The management largely involves the treatment of musculoskeletal complications which vary with age of onset and severity. However, trials of treatment are ongoing with sodium valproate, one of several agents which increases transcription from the *SMN2* gene, which may slow progress of the condition.

Ventilatory support may be necessary in SMA II. Invasive respiratory support leads to improved survival in some patients. Non-invasive ventilation may be necessary if nocturnal hypoventilation develops. Scoliosis develops if there has been paraspinal weakness prior to the growth spurt and spinal correction may be necessary to preserve mobility and ventilatory function. The provision of walking aids including braces and callipers may allow younger patients to remain ambulant for many years.

Disorders of the neuromuscular junction

Functional or structural abnormalities of the neuromuscular junction (NMJ) interfere with the transmission of neural impulses from motor nerves to muscles. In myasthenia gravis, antibodies mediate damage to the post-synaptic acetylcholine receptor. In Lambert–Eaton myasthenic syndrome, antibody-mediated block of the pre-synaptic calcium channels results in a deficit of quantal release. Congenital myasthenia is caused by defects affecting pre-synaptic, synaptic and post-synaptic mechanisms leading to NMJ impairment.

Myasthenia gravis

Myasthenia gravis (MG) is an autoimmune disorder caused by antibodies directed against the acetylcholine receptor (AChR) in the muscle membrane (Figure 9.13). The serum antibody to the AChR and its interaction with the target antigen are well characterized.

The nicotinic AChR is a transmembrane glycoprotein with five subunits arranged around a central ion channel. These subunits are designated α, β, δ, γ and ε, each of the two α units has an extracellular acetylcholine binding site. The fetal AChR has a γ subunit in place of the ε. The AChR ion channel is closed in the resting state and when the binding sites of both α-subunits are occupied the channel opens transiently. There is a continuous process of turnover and renewal of AChR at the NMJ; impaired transmission induces increased transcription of AChR genes, which eventually allows full recovery of the NMJ.

IgG anti-acetylcholine receptor antibodies (AChRAb) are detectable in 75% of patients with MG. These antibodies bind to the receptor leading to blockade and cross-link muscle surface AChR increasing their rate of internalization or bind complement leading to destruction of the muscle end-plate. Loss of voltage gated Na^+ channels at the end-plate leads to reduced muscle membrane depolarization and an increase in the threshold necessary to initiate a muscle action potential.

'Antibody negative' myasthenia gravis

20–25% of patients with MG are AChRAb negative, known as seronegative MG (SNMG). IgG auto-antibodies to muscle-specific kinase (MuSK) can be found in >50% of ocular/generalized SNMG. MuSK is a receptor tyrosine kinase expressed

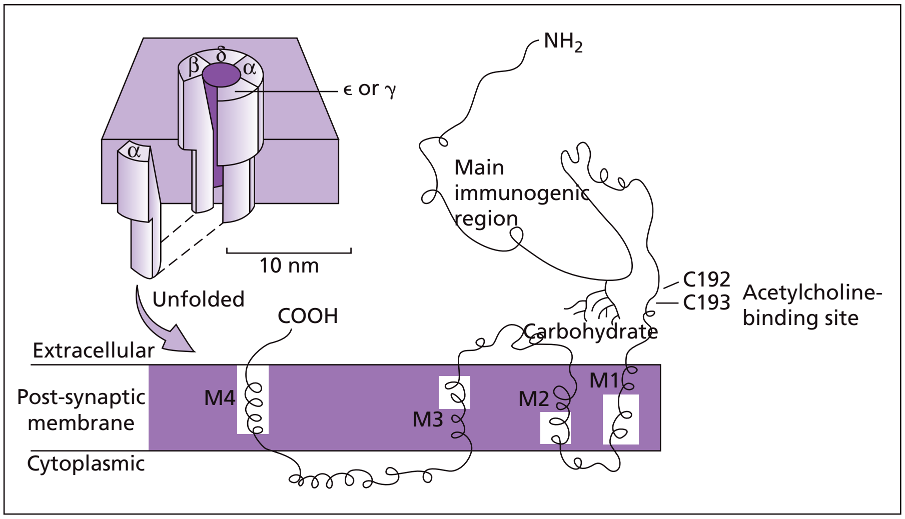

Figure 9.13 The acetylcholine receptor. The subunits of the acetylcholine receptor – α, β, γ, δ or ε are arranged like barrel staves around the central ion pore. Each subunit winds through the junctional membrane four times (sites M1, M2, M3 and M4). In the unfolded view of the subunit, the amino-terminal end of the subunit is extracellular, where it is accessible to acetylcholine, which binds at the site shown (amino acids 192 and 193). In myasthenia gravis, autoantibodies may bind to various epitopes of all subunits, but a high proportion of antibodies bind to the main immunogenic region of the subunit. (From Drachmann DB. *N Engl J Med* 1994; 330: 1797 with permission.)

Table 9.26 Drugs that impair neuromuscular transmission.

Antibiotics	Aminoglycosides (gentamicin, neomycin, streptomycin)
Antiarrhythmics	Quinine, quinidine, lidocaine and β-blockers
Antiepileptics	Phenytoin
Antirheumatoid drugs	D-penicillamine
	Chloroquine
Competitive neuromuscular junction blocking agents used during anaesthesia	D-tubocuarine
	Pancuronium
	Depolarizing agents (e.g. succinylcholine)

selectively in skeletal muscles. It helps cluster post-synaptic proteins, including AChR at the NMJ. Anti-MuSK antibodies may activate complement inducing lysis of the post-synaptic membrane.

Clinical features

MG has a bimodal pattern of onset; it occurs most commonly in women in the second and third decade but there is a second peak of incidence in the sixth and seventh decades with men being predominantly affected. Presentation is characterized by fatigable weakness in the ocular, cranial nerve, limb or truncal musculature.

A number of drugs may impair neuromuscular transmission and therefore precipitate or exacerbate myasthenic weakness; these are summarized in Table 9.26. D-penicillamine MG is usually mild and may remit when the drug is withdrawn; however, in others it may precipitate severe MG which proves difficult to control.

The initial manifestation is often fatigable visual blurring, diplopia and/or unilateral or asymmetrical ptosis which worsens towards the end of the day. Weakness remains localized to the ocular muscles in 15% of patients. The jaw, facial muscles, speech and/or swallow, neck, respiratory muscles and proximal limbs are all commonly affected. Selective diaphragm weakness is rare.

On examination, fatigable weakness can be demonstrated in any affected muscle by repetitive or sustained activity. Cogan's lid twitch sign is pathognomic. Cooling of the eye with an ice pack may lead to improvement in ptosis but its sensitivity and specificity in myasthenia remain uncertain. The ophthalmoplegia is fatigable and often does not fit the pattern of a single cranial nerve weakness. The medial and inferior rectus and superior oblique are most commonly affected but severe and occasionally total ophthalmoplegia may occur.

Respiratory muscle weakness is demonstrated by limited chest wall movement and excessive use of accessory muscles of respiration. Weakness of the truncal musculature leads to difficulty sitting from supine while limb weakness is characterized by fatigability in a limb girdle pattern. However, it may be markedly asymmetrical and occasionally distal musculature may be preferentially affected.

The anti-MuSK phenotype has a predominantly facial, bulbar and respiratory muscle weakness, often occurring in young female patients.

A differential diagnosis is summarized in Table 9.27. Myasthenia can coexist with other autoimmune diseases such as rheumatoid arthritis, pernicious anaemia, SLE, vitiligo and thyroiditis.

Diagnostic tests

The diagnosis of MG can be supported by clinical, laboratory and electrophysiological investigations.

An intravenous bolus of edrophonium may transiently improve the symptoms and signs of myasthenia and is the basis of the Tensilon test. However, false negatives are common, false positives occur with many other neuromuscular diseases, and it is contraindicated in the elderly or patients with cardiac disease.

Table 9.27 Differential diagnosis of myasthenia.

Ophthalmoplegia	Isolated cranial nerve palsies Thyroid eye disease Guillain–Barré syndrome Mitochondrial disease Oculopharyngeal muscular dystrophy Central causes (e.g. aneurysms, MS)
Bulbar and respiratory weakness	Acid maltase deficiency Motor neurone disease, Kennedy's disease Central causes (e.g. tumour, stroke and MS)
Proximal limb weakness	Myopathy including 'limb girdle', congenital myasthenia; inflammatory causes (e.g. polymyositis), LEMS

LEMS, Lambert–Eaton myasthenic syndrome.

Because neuroimmunological and electrical tests are now available the Tensilon test is often unnecessary.

Electrophysiological studies looking at repetitive stimulation and single fibre EMG (SFEMG) are abnormal in MG. Repetitive stimuli at a rate of 3 Hz lead to a decrement in the CMAP amplitude of >15% which should be reproducible. SFEMG is the most sensitive neurophysiological investigation of neuromuscular transmission. An increase in jitter may be restricted to the ocular or facial muscles. However, SFEMG is not specific and jitter may be seen in other disorders of the NMJ, nerve or muscle.

AChRAb are detected in approximately 75% of patients with generalized myasthenia and 50% with pure ocular myasthenia. AChRAb are the most specific marker for MG but they may be found in association with thymoma, SLE, autoimmune liver disease, inflammatory neuropathies and rheumatoid arthritis (especially when taking penicillamine) without any clinical evidence of myasthenia. Levels of AChRAb fluctuate with disease severity in an individual patient.

Anti-striated muscle antibodies are present in approximately 25% of patients with MG but up to 90% with concurrent thymoma. Anti-MuSK antibodies occur in >50% of SNMG cases and are not found in AChRAb positive MG cases. Other autoantibodies that may be present in myasthenia include anti-smooth muscle, antinuclear, antithyroid antibodies as well as rheumatoid factor and antibodies to gastric parietal cells and red blood cells.

Management

There are few randomized controlled trials in MG but treatment is based on clear principles which are determined by the age, sex, disease pattern and severity, the risk of side-effects and the availability of close clinical and investigational monitoring. Treatment may be symptomatic (anticholinesterases), disease modifying (immunosuppression with steroids, immunosuppressant drugs, immunoglobulins or plasma exchange) and/or surgical (thymectomy).

Anticholinesterases are the first line of treatment. They are of value in the early symptomatic treatment of MG as a single therapy or later as an adjunct to immunotherapy. Pyridostigmine is the most widely used. Side effects of anticholinesterases include muscle fasciculations and weakness occurring as a result of excessive stimulation of the nicotinic acetylcholine receptors. The abdominal cramps, diarrhoea, increased bronchial and oral secretions can be mitigated by antimuscarinic medication. Persistence of myasthenic weakness despite increasing doses of pyridostigmine is an indication for immunosuppressant treatment.

Corticosteroids can be extremely effective in improving myasthenic weakness and establishing remission. There is considerable variability in dosage, duration of treatment and clinical response to steroids. They should be commenced in hospital because of the significant risk of deterioration in proximal strength during the first 2 weeks of treatment. The risk is reduced if an incremental dosage is used. Marked improvement will occur in more than 50% of patients and remission in 25% with the time to maximum benefit approximately 6 months. Only 5% will show no significant improvement. While steroids are effective and inexpensive, their use is limited by considerable toxicity and they should be weaned to the lowest dosage possible to prevent glucocorticoid side effects. All patients likely to receive more than 7.5 mg/day steroid for more than 6 months should be treated to prevent iatrogenic osteoporosis, preferably with a bisphosphonate.

Azathioprine has been shown to reduce the dosage of prednisolone required to maintain remission and to reduce the number of treatment failures. The effects of azathioprine (<2.5 mg/kg) are extremely slow to develop and a therapeutic dosage may take up to 2 years for the full clinical effect to be seen. The risk of azathioprine toxicity may be reduced by screening for the activity of the enzyme thiopurine methyltransferase (TPMT) which metabolizes azathioprine. The risk of myelosuppression is increased in those with low activity.

Ciclosporin has also been shown to be effective in a randomized controlled trial. Ciclosporin has similar efficacy to azathioprine but works more rapidly. Its use is limited by significant side effects including nephrotoxicity and hypertension which contraindicate its use in pre-existing renal disease and necessitate the need for regular blood monitoring. Cyclophosphamide is now rarely used in MG because of its toxicity. Mycophenolate has recently been used as an alternative second line immunosuppressant agent if azathioprine has been ineffective or not been tolerated. It is well tolerated with relatively few side-effects.

Plasma exchange reduces AChRAb titres significantly but is often ineffective in SNMG. It is valuable in producing short-term improvement of severe myasthenic weakness but difficulties and complications of venous access, biochemical derangements and high overhead costs limit its use. IVIG is similar in efficacy to plasma exchange and is valuable in producing short-term improvement in myasthenic crisis and also occasionally as a long-term maintenance therapy.

Thymectomy has been used in the treatment of MG for 50 years. Approximately 15% of patients with MG have a thymoma (Figure 9.14) while up to 50% of patients with thymoma will develop myasthenia which may occur even after thymectomy. CT or MR imaging of the mediastinum should be undertaken

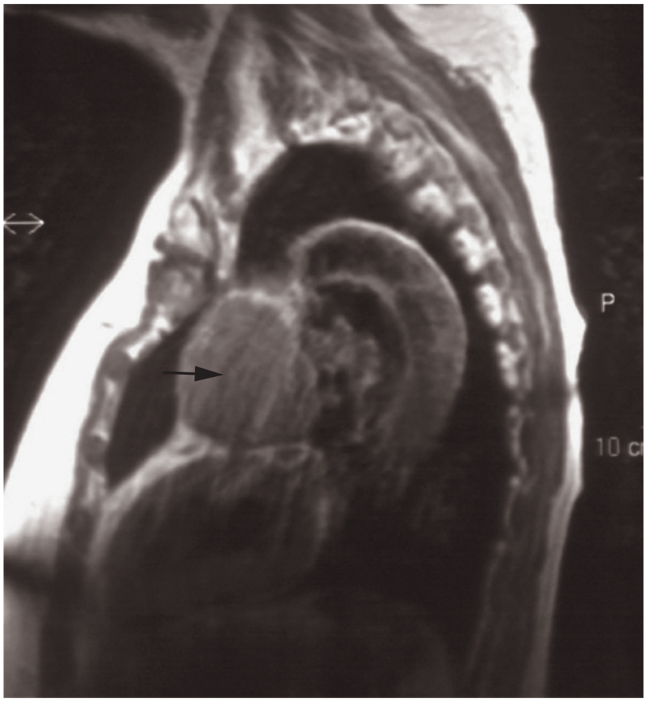

Figure 9.14 Large anterior mediastinal thymoma in an 80-year-old patient with mild generalized MG (MRI T2W).

in all patients with MG to exclude thymoma. Most are benign and encapsulated; however, 10% show malignant features with invasion of the capsule, local spread, seeding or even distant metastasis. Postoperative radiotherapy is generally recommended for invasive thymoma in which the tumour capsule has been penetrated. If metastatic spread has occurred, chemotherapy may be highly effective with varying regimes including cyclophosphamide, vincristine, cisplatin and doxorubicin proving effective, not just in reducing the thymoma, but also in controlling the myasthenia.

Objective evidence of the efficacy and role of thymectomy remains elusive. Evidence from open studies indicates thymectomy for non-thymomatous autoimmune MG increases the probability of remission or improvement. Up to 46% of patients with thymic hyperplasia may achieve full remission within 2–5 years of surgery and significant improvement and reduced treatment will be seen in up to 40%. Thymectomy is indicated for patients with seropositive MG from late childhood up to the age of 60 years. In those over 60 years, those with seronegative or ocular MG the role of thymectomy is less clear.

Ocular myasthenia gravis

In about 15% of MG the disease remains localized to the orbicularis oculi and extraocular muscles although EMG may show generalized NMJ abnormalities. Remission may occur in up to 20%. Response to anticholinesterases is often disappointing. Immunosuppression with steroids and azathioprine may be necessary if ptosis or diplopia are symptomatic.

Pregnancy and myasthenia

The effects of pregnancy on the patient and fetus should be considered separately. Myasthenia may worsen, improve or remain stable during pregnancy but there is a significant risk of deterioration in the puerperium. Pregnancy should ideally be planned when the patient is strong, steroids should be maintained at the lowest therapeutic dosage and, if possible, other immunosuppressants should be avoided. If pre-eclampsia occurs, magnesium sulphate should not be used because of the risk of further impairment of NMJ transmission.

The newborn is at risk of transient neonatal myasthenia which occurs in about 10% of myasthenic pregnancies. This condition is caused by transmission of anti-acetylcholine receptor antibody across the placenta.

Myasthenic crisis

Myasthenic crisis indicates the development of ventilatory failure. Approximately 20% of patients with MG will develop myasthenic crisis and, in up to 10%, there may be more than one episode. Respiratory failure in MG may be precipitated by bronchopneumonia, systemic sepsis, medication, surgery or inadequate treatment often related to a rapid tapering of the steroid dosage. Rarely, cholinergic crisis or the commencement of high-dose corticosteroids is to blame. In acute respiratory failure urgent elective tracheal intubation and ventilation should be considered when the vital capacity falls below 15 mL/kg. The rate of progression, the presence of bulbar weakness and the state of the patient are also crucial to the decision (see Chapter 19).

Cholinergic crisis

Cholinergic crisis is rare but should be suspected in patients taking high doses of anticholinesterase medication who have extensive cholinergic side effects. It may be necessary to admit the patient to ITU, intubate and ventilate and withdraw all anticholinergic medication.

Anaesthesia and peri-operative care

Because myasthenic crisis may be precipitated by anaesthesia, the stress of surgery or non-depolarizing neuromuscular blocking agents, elective surgery should be undertaken with experienced anaesthetic support following pre-operative plasma exchange or IVIG if necessary.

Other causes of abnormal neuromuscular transmission

Snake venoms, tick paralysis and toxic agents including organophosphates may affect neuromuscular transmission. Organophosphates (OPs) are used as nerve agents (Chapter 18) but are also widely employed as pesticides. Exposure may be occupational, food-borne or as a consequence of suicide attempts. Acute exposure results in cholinergic crisis. Respiratory muscle weakness is resistant to atropine and intubation is required. Longer term OP exposure may lead to a myasthenic syndrome or an axonal sensory motor neuropathy. Rarely, OP toxicity may cause late onset of neuropsychiatric and cognitive impairment or a parkinsonian syndrome.

Table 9.28 Causes of congenital myasthenia.

Pre-synaptic defect	
Reduced synaptic vesicles	Autosomal recessive
Failure of ACh resynthesis or packaging (choline acetyltransferase deficiency)	
Lambert–Eaton-like CMS	
Synaptic defect	
End-plate ACh deficiency	Autosomal recessive
Post-synaptic defect	
Acetylcholine receptor deficiency	Autosomal recessive
AChR mutation	
Rapsyn mutation	
Plectin deficiency	
Acetylcholine receptor kinetic abnormality	Autosomal dominant > autosomal recessive
Channelopathies	
Slow channel	
Fast channel	
Sodium channel	

ACh, acetylcholine; AChR, acetylcholine receptor; CMS, congenital myasthenia syndrome.

Congenital myasthenia

Congenital myasthenic syndromes (CMS) are caused by inherited abnormalities of the NMJ that interfere with normal synaptic transmission. The conditions are rare but important to distinguish from SNMG because of the implications for management and genetic advice. In most patients there is a malformation in the structure or function of the pre- or post-synaptic NMJ although congenital acetylcholine deficiency may occur. The classification of CMS is summarized in Table 9.28. Abnormalities of post-synaptic function are most common.

Clinical features

CMS may present in infancy with hypotonia, failure to thrive, delayed motor milestones and unexplained apnoeic episodes. In children and adults the conditions are manifest as fatigable or fluctuating, ocular, facial and bulbar weakness although limb and truncal wasting and weakness may also be prominent. The weakness tends to progress during adolescence but then often stabilizes. There may be episodic worsening of the weakness, possibly triggered by intercurrent events such as pyrexia. On examination there is fatigable muscle weakness on exertion but a prominent myopathy and scoliosis may be present. Distal weakness, ocular and pupillary abnormalities are also occasionally present. There may be a positive family history. In infancy CMS may mimic muscular dystrophy, congenital and metabolic myopathy, spinal muscular atrophy or structural brainstem anomalies. In children and adults it is necessary to distinguish CMS from SNMG, forms of MND, LGMD and neuropathies.

Investigation

Standard MG investigations document an abnormality at the NMJ. Confirmatory diagnostic evidence comes from morphological and genetic NMJ studies. These include microelectrode recordings of miniature end-plate potentials to nerve stimulation, EM studies of intercostal muscle AChR density studies using iodine-123 labelled bungarotoxin, patch clamp studies of individual channels at the NMJ and genetic studies of target genes in the AChR and post-synaptic structure. There is no definitive treatment.

Lambert–Eaton myasthenic syndrome

Lambert–Eaton myasthenic syndrome (LEMS) is a rare disorder caused by impaired release of ACh by the presynaptic terminal of the NMJ. It is associated with underlying malignancy or autoimmune disease. LEMS is characterized by weakness and fatigue.

Clinical features

The onset is often insidious with the gradual development of progressive weakness and fatigue. The condition may occur at any age but is more common after 40 years. Underlying malignancy may be present in up to 50% of patients although this may not become apparent until more than 4 years after the onset of LEMS.

Fatigue is prominent at presentation. Weakness may affect the proximal muscles, particularly the legs and is often associated with aching and stiffness. Autonomic features including dry mouth, constipation and impotence are also common. Ophthalmoplegia, ptosis, bulbar and respiratory muscle weakness can occur but are less common than in seropositive autoimmune MG. Examination findings are characterized by proximal weakness with a fatigable component. Reflexes are reduced or absent but after a short period of sustained effort they become brisker showing the phenomenon of post-tetanic potentiation.

The most common underlying tumour is small cell lung cancer (>80%) but LEMS has also been reported in association with lymphoproliferative disorders, malignant thymoma and rarely with carcinoma of the breast, stomach, colon, prostate, kidney and bladder.

Aetiology

LEMS is an autoimmune disorder driven by antibodies to the voltage gated calcium channel (anti-VGCC Ab) of the presynaptic terminal. Serum from up to 90% of patients with paraneoplastic and autoimmune LEMS contain anti-VGCC Ab. In patients with small cell lung cancer it is likely that cancer cells contain antigen which mimics VGCC and induces the production of antibodies while the mechanism of production in the autoimmune condition is unclear.

Investigations

The diagnosis of LEMS is established by the presence of anti-VGCC antibodies and by characteristic electrophysiological findings. A small CMAP, a decremental response to repetitive stimulation at low frequency (1–5 Hz) and an increment following sustained maximum voluntary contraction or 20–50 Hz repetitive stimulation are typical. SFEMG shows increased jitter and block.

A search for underlying malignancy and in particular small cell lung cancer must be conducted including FDG-PET if necessary. Malignancy negative LEMS patients should be closely followed up as an underlying tumour may become apparent after a long latent period.

Treatment

Any underlying carcinoma must be appropriately treated. Successful treatment often leads to improvement in LEMS.

Specific treatment is directed towards facilitation of neuromuscular transmission, removal of the antibody or suppression of its production. Pyridostigmine has a mild effect in enhancing neuromuscular transmission but most patients require 3,4 diaminopyridine which blocks presynaptic K^+ channels, lengthens depolarization of the nerve terminals and increases quantal ACh release. It is associated with paraesthesiae, anxiety and insomnia and an increased risk of seizures. If severe weakness persists despite these treatments immunomodulation treatment is indicated. The response to plasma exchange and IVIG is less reliable than in MG. Prednisolone, azathioprine and ciclosporin are all effective in LEMS.

Muscle diseases

The understanding of muscle disease has undergone a revolution in the last 20 years as a result of advances in immunohistochemistry and genetics which now allow accurate diagnosis of most of the inflammatory, genetic and metabolic muscle diseases. Many muscle diagnoses are now being revised as new knowledge becomes available.

Basic muscle biology

Muscle is a complex assembly of interacting proteins. Its principal function is to respond to a stimulus from a motor neurone by physically shortening its contractile apparatus with the conversion of electrical and chemical to mechanical energy.

The basic unit of a striated muscle is the myofibril. The myofibril is made up from many repeating functional multiprotein complexes of actin, myosin and titin called sarcomeres, the smallest functional unit of muscle. Thousands of sarcomeres are arranged end-to-end, giving muscle its striated microscopic appearance. Together these form the contractile apparatus. ‘Thin’ filaments of actin and ‘thick’ myosin filaments are arranged such that they may slide over each other, retaining their own length but shortening the sarcomere as the thin filaments are pulled towards the centre. The sarcomeres and myofibrils are enveloped in the mesh-like structure of the sarcoplasmic reticulum, which is central to excitation–contraction coupling.

In its simplest terms, electrical stimulation of the muscle cell causes a release of calcium ions from the intracellular sarcoplasmic reticulum. This in turn activates the contractile apparatus (Figure 9.15a) and an energy-dependent interaction occurs between the actin and myosin filaments of the sarcomere. As calcium levels fall, the interaction between actin and myosin ends, the sarcomere extends again and so the muscle relaxes.

Together with the sarcomere is an array of other structures. First, a series of structural proteins anchor the contractile apparatus within the sarcomere (Figure 9.15a). A number of further proteins then link the sarcomere to the cell membrane (the sarcolemma) and extracellular matrix (Figure 9.15b). Dystrophin is attached at one end to actin and at the other to a complex of glycoproteins (including, amongst others, the dystroglycans, sarcoglycans and laminin) that are closely associated with the sarcolemma. In addition, various ion channels span the cell membrane, and their role in moderating the influx and efflux of potassium, sodium, calcium and chloride is crucial to proper muscle function.

Muscle is a complex structural and functional unit. Genetic or acquired abnormalities of any of the proteins or processes above may result in disease. However, muscle is also highly metabolically active tissue and so is vulnerable to any derangement of energy release. Disorders of metabolism (carbohydrate, lipid, oxidative phosphorylation) therefore form the other fundamental basis of muscle disease.

Clinical assessment of the patient with muscle disease

Some muscle diseases such as Duchenne muscular dystrophy, myotonic dystrophy or inclusion body myositis can often be confidently diagnosed at the bedside. For the remainder, the clinical assessment of patients remains paramount. Although diagnostic investigations for suspected muscle disease have never been so powerful, notably with the ability of DNA testing to confirm the presence (or absence) of a disease-causing genetic defect, further evaluation must be guided appropriately by the differential diagnosis generated from the findings of the history and examination.

History

The primary focus of any history is on the particular complaint of the patient. The most fundamental symptoms of muscle disease are given in Table 9.29. It is crucial to ensure that what the patient reports is, in fact, what he or she means. This is not always an easy task. ‘Weakness’ may refer to stiffness, tiredness or pain. Persevere.

As with all disease where the differentiation of genetic from acquired disease is important, the date of symptom onset is very useful. Open questioning may reveal the perceived onset. Subsequent specific questions should be asked about the patient’s antenatal history, birth, developmental milestones, sporting ability and achievements and general health in youth. The onset may regress by a decade or two.

Pigmenturia (try ‘coca-cola urine’) should be specifically asked for, together with any provocation and whether it was associated

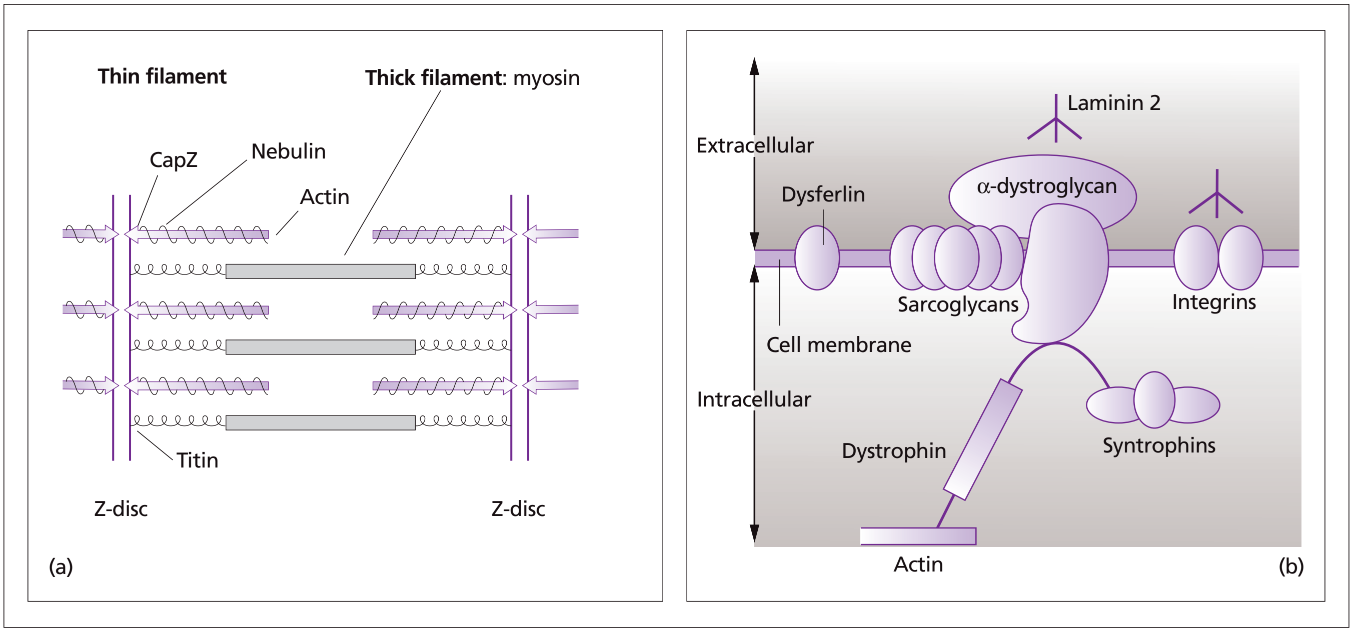
Thin filament
Thick filament: myosin
CapZ
Nebulin
Actin
Titin
Z-disc
Z-disc
(a)
Laminin 2
Extracellular
α-dystroglycan
Dysferlin
Sarcoglycans
Integrins
Cell membrane
Intracellular
Dystrophin
Syntrophins
Actin
(b)

Figure 9.15 (a) Simplified schematic representation of muscle contractile apparatus. Thin filaments are comprised of actin molecules as the core, wrapped in the template protein, nebulin, plus troponin and tropomyosin (latter two not shown). They are capped at the Z-disc with CapZ and at the other end with tropomodulin (not shown). Thick filaments of myosin are bound by titin to the Z-disc. One element of titin is elastic. Contraction involves interaction of thick and thin filaments so latter move towards centre. (b) Simplified schematic representation of muscle cell membrane and associated non-neuromuscular junction proteins. (Some components omitted for clarity.)

Table 9.29 Issues important in history-taking in muscle disease.

Symptom	Details
Weakness	Confirmation of reduced strength and function Onset, duration and progression Assessment of degree of weakness and subsequent disability, e.g. date of first use of walking aids Pattern of muscle involvement – proximal limb (reaching objects from shelves, standing from sitting) versus distal limb (opening jars or bottles, tripping over) versus selective focal Variability and, if present, exacerbating or relieving factors (always consider the possibility of fatigability)
Pain	Confirmation of myalgia, rather than, for example, impaired sensation Localized versus generalized Severity Precipitating, exacerbating or relieving factors Association with any other symptom
Cramps	Localised versus generalised Precipitating, exacerbating or relieving factors Association with any other symptom
Stiffness	Identification of specific failure of relaxation (myotonia), e.g. difficulty releasing grip or opening eyes Localized versus generalized Exacerbating or relieving factors
Fatigue	Distinction from other symptoms Precipitating, exacerbating or relieving factors
Pigmenturia	Precipitating factors Association with any other symptom

with other symptoms. Some patients may have had solitary or only infrequent episodes.

Paroxysmal or variable symptoms (e.g. cramps, spasms, stiffness – and more specifically myotonia) require further questions, seeking to identify provoking, exacerbating or relieving factors. Such influences may be crucial in refining the clinical features of a channelopathy.

Other relevant systems need to be enquired about, with particular attention paid to cardiac symptoms (palpitations, exertional dyspnoea, ankle swelling and paroxysmal nocturnal dyspnoea) and respiratory complaints (especially any suggestion of neuromuscular compromise, often first manifest as unrefreshing sleep, orthopnoea, morning headache or daytime tiredness). A suspected multi-system condition requires attention be paid to other possible involvement (e.g. the rash of dermatomyositis or deafness in mitochondrial disease).

The history should also document the current function of the patient (working from head to toe). This semi-quantification is useful to assess any change over time, and also in answering specific questions later (as typically generated by welfare benefit assessments, driving licence reviews and other bureaucratic agencies).

Assessment of the past medical history is directed at identifying other conditions that may either cause muscle symptoms (e.g. rheumatological or endocrine disease), mimic them or make their assessment or treatment more difficult (e.g. orthopaedic conditions or a peripheral neuropathy). Specific questions should be asked about any difficulties with anaesthesia. Myotonic dystrophy may first be revealed by peri-operative cardiac arrhythmia or difficulty weaning from a ventilator, while certain myopathies, notably central core disease but also the dystrophinopathies, can lead to malignant hyperthermia reactions. A thorough medication history is also required, including over-the-counter preparations, alternative remedies and recreational drugs, and any temporal association with symptoms explored.

Examination

As part of a complete neurological examination, this should follow the classic procedure of inspection, palpation and assessment of power and function, with certain particular measures in addition, such as testing for myotonia. Inspection should be focused on assessment of muscle bulk (palpation can identify subtle wasting, and also note textural differences in muscle), any involuntary movements (fasciculation, myokymia, myotonia) and any skeletal abnormalities (e.g. scapular winging, kyphoscoliosis).

Power assessment may well require additional examination techniques to those routinely employed. Subtle facial weakness can be revealed by formally testing eyelid and lip closure. Speech gives a good indication of lingual and palatal function and specific requests for buccal, palatal and lingual consonant production in addition to a demonstration of a cough (see below) and a sustained note can indicate more specific impairments. Neck extension and flexion should be tested with the patient both lying and upright. Neck power patterns can be very revealing.

Table 9.30 Simple bedside functional motor tests.

Lifting head from lying down
Straight leg rising from lying down
Standing from lying down and/or squatting and/or sitting
Ability to walk on heels or on tiptoes
Ability to hop on one foot
Ability to run
Time to walk a specified distance
Time to climb a flight of stairs
Raising arms above head

Experienced clinicians learn that muscle strength testing needs appreciation of the confounding actions of suboptimal effort ('give-way' weakness) or when pain is a limitation. Accordingly, bedside tests of disability rather than impairment can give a more useful guide, particularly on serial examinations, to assess disease progression or treatment effect when impairment testing is not so reliable (Table 9.30).

Myotonia should be tested by sustained grip or eyelid closure, and/or by percussion of appropriate muscles (e.g. thenar eminence, forearm or even the tongue). Respiratory function can be assessed by looking for abdominal paradox on deep inspiration and expiration (the abdomen normally distends on inspiration), plus specific assessment of sniff and cough strength. Spirometry allows quantification of respiratory function, with the caveat that poor effort and air leak resulting from facial weakness must be taken into consideration.

Investigation of muscle diseases

Creatine kinase

This enzyme is continuously released at low level in to the circulation, a process increased by any injury to muscle or by excessive activity. In addition, there is considerable variation in CK levels across a normal population. CK is proportional to the muscle bulk of an individual, and routine exercise and alcohol will increase the levels. Furthermore, values in Afro-Caribbean and Asian populations are higher. Thus, the CK result should be interpreted in the light of an appropriate normal range. Quantification of different isozymes (e.g. myocardial CK-MB) is not of use, although it should be noted that other enzymes may be released from muscle (such as AST). Finally, some muscle disorders (notably myotonic dystrophy) do not usually cause CK to be elevated.

Neurophysiology

Needle EMG can be helpful in distinguishing myopathy from an otherwise indistinct lower motor neurone pattern of weakness. The classic findings in myopathy are spontaneous activity with fibrillations, positive sharp waves and complex repetitive discharges plus polyphasic, low amplitude, short duration units on voluntary contraction. This pattern is common to several underlying processes and neurophysiological examination is less useful in refining the diagnosis of muscle disease than when used to investigate neuropathy. Other electrophysiological phenomena may be seen, such as myotonia – sustained activation, while specialized serial examination after cooling a limb, or after exercise of varying duration, forms a crucial element in assessing possible channelopathies.

Muscle biopsy

Muscle biopsy is often the keystone of diagnosis. It should be considered and, if possible, performed in all cases before any treatment is initiated. Close liaison with the pathologist and technician is essential because experience in both the preparation of biopsy material and its microscopic evaluation is critical. Practically this may necessitate sending the patient or the biopsy specimen material to a specialist centre. The muscle selected should ideally be moderately involved. Pathologists often have particular experience with certain muscles and this should influence the choice.

Initial histological diagnosis is based on the presence or absence of inflammatory change, necrosis, fibre atrophy or other structural change (vacuoles or inclusion bodies). Enzyme stains may identify certain conditions (e.g. absent acid phosphorylase in McArdle's disease, or reduced cytochrome oxidase staining in mitochondrial disorders). Immunostaining for various structural proteins (e.g. dysferlin, desmin and the sarcoglycans) have greatly improved the diagnosis of the dystrophies, as patterns of reduced or altered expression have been identified. If required, EM may detect more subtle abnormalities (glycogen molecules, or features of mitochondrial disease not otherwise apparent).

Metabolic testing

Exercise testing (most safely performed non-ischaemically), with serial collection of blood samples for lactate and ammonia levels in normal subjects generates a three- to fivefold increase in both. However, in glycolytic or glycogenolytic disorders, the lactate rise is reduced (or absent) with excessive elevation of ammonia. Myoadenylate deaminase deficiency, by contrast, causes a normal rise in lactate but no change in ammonia. Specialized centres can perform analysis of other enzyme function in biopsied muscle, such as the mitochondrial respiratory chain or carnitine metabolism.

Genetic testing

Specific DNA analysis has revolutionized diagnosis of muscle disease. In some conditions of distinctive clinical appearance (e.g. myotonic dystrophy or facioscapulohumeral muscular dystrophy [FSHD]), it can form the first step in investigation, possibly sparing the patient more invasive tests. In other situations, such as the limb girdle dystrophies, genetic testing should be appropriately guided by other findings, notably the muscle biopsy.

Genetic muscle diseases

The clinical practice and understanding of genetic muscle disease is changing rapidly as a direct result of the wealth of recent molecular genetic discoveries. Approximately 1/6000–7000 of the UK population has one of many diverse genetically determined muscle diseases. Duchenne muscular dystrophy, caused by mutations in the dystrophin gene, is a young onset severe progressive muscle wasting disease which can be lethal in late teens without appropriate respiratory and cardiac support. In contrast, some myopathies caused by mutations in mitochondrial DNA can develop in late adult life manifesting as external ophthalmoplegia or mild proximal myopathy with a relatively indolent course. The mortality in genetic muscles diseases is often determined by the degree of cardiac and/or respiratory muscle involvement and therefore cardiorespiratory screening is essential in the assessment of patients presenting with suspected genetic muscle disease. Careful clinical evaluation and attention to the family history will reduce the differential diagnosis sufficiently to rely on direct genetic testing alone. Sometimes EMG and muscle biopsy may not be required. Where the distinction between inflammatory and genetic myopathy is difficult, genetic testing may now be helpful in resolving it. In a specialist muscle service one sees many cases where prominent inflammatory infiltrates on biopsy have led to the erroneous diagnosis of polymyositis in patients subsequently shown genetically to have dysferlinopathy or FSHD.

Where a precise DNA-based diagnosis is possible patients and families can be provided with accurate prognostic and genetic counselling information and entered into a rational screening programme for recognized complications. As national networks for DNA-based diagnosis become available more patients will have access to this diagnostic precision.

Genetic testing is now often the first investigation in myotonic dystrophy and FSHD and, if positive, muscle biopsy is often not required. In other more heterogeneous genetic muscle diseases, such as limb girdle muscular dystrophy (LGMD), muscle biopsy with careful immunohistochemical analysis is usually required to direct gene testing. However, as gene sequencing technologies become increasingly available even LGMD gene analysis may be selected at an earlier stage in the diagnostic process.

In this section we mention the more common genetic muscle diseases (Table 9.31) encountered by adult neurologists. The aim is to describe clinical features and to suggest an efficient diagnostic strategies (Table 9.32). DNA-based diagnosis may accelerate and simplify the diagnostic process, thereby providing the most accurate information for patients with these diseases.

Muscular dystrophies

Many genes causing different muscular dystrophies have been discovered in recent years. The causative proteins have various functions; dystrophic muscle may be the relatively non-specific end result of a number of different pathogenic pathways. The proteins identified to date include sarcolemmal structural proteins (e.g. dystrophin, sarcoglycans and dysferlin), nuclear envelope proteins (emerin, lamin a/c), enzymes (calpain, fukutin-related protein), sarcomeric proteins (myotilin) and extracellular matrix proteins (laminin, collagen type 6; Figure 9.15b). For some disorders, such as myotonic dystrophy, a single gene accounts for most cases and a simple gene test is available. In contrast, for other disorders, such as LGMD, the situation regarding testing is more complex because of genetic heterogeneity.

Xp21 dystrophies: the dystrophinopathies

Dystrophin is a major muscle cell structural protein that lies just below the sarcolemma and helps to stabilize the sarcolemma during muscle contraction. It links intracellular actin to a complex set of transmembrane proteins which in turn link to elements of the extracellular matrix (particularly to an extracellular protein called laminin). Genetic defects in the dystrophin protein are associated with two major phenotypes: Duchenne and Becker muscular dystrophy.

Table 9.31 Genetic muscle diseases.

- Muscular dystrophies
  - Dystrophinopathies
  - Emery–Dreifuss muscular dystrophy
  - Limb girdle muscular dystrophies
  - Facioscapulohumeral muscular dystrophy
  - Oculopharyngeal muscular dystrophy
  - Congenital muscular dystrophy
  - Myotonic dystrophy
- Bethlem myopathy
- Distal myopathies
- Congenital myopathies
- Myofibrillar (desmin) myopathies
- Skeletal muscle channelopathies
- Metabolic myopathies
  - Mitochondrial myopathies
  - Glycogen storage myopathies
  - Lipid storage myopathies

Duchenne is an aggressive and lethal dystrophy affecting boys in which there is a severe reduction in the amount of the dystrophin protein in muscle. To date there is no curative treatment, but improved ventilatory support has recently been shown to increase the quality of life and life expectancy.

Becker muscular dystrophy is more likely to be encountered in adult muscle practice. Severity correlates with the amount of dystrophin protein present. Becker patients present as a limb girdle pattern of muscle weakness with pseudohypertrophy of calf muscles. Cardiomyopathy is an important complication; occasionally, severe dilated cardiomyopathy may be the presenting feature.

Diagnosis can be achieved by genetic testing. However, most testing protocols only screen a proportion of the gene as it is so large. Therefore a 'negative' genetic test does not exclude the diagnosis. A muscle biopsy with dystrophin immunohistochemical studies may therefore be required.

Genetic counselling in families as for an X-linked recessive disease is important but one-third of dystrophinopathy cases represent new mutations without family history. Female carrier status may be ascertained by dosage-sensitive polymerase

Table 9.32 Diagnostic strategies for inherited myopathies.

Condition	DNA based diagnosis available?	Muscle biopsy needed?
Xp21 dystrophies (dystrophinopathies)	Yes, but negative gene test does not exclude diagnosis	Yes, if genetic test negative
Emery–Dreifuss muscular dystrophy	Yes, but usually only after immunohistochemistry for lamin a/c and emerin	Yes, muscle biopsy remains important
Limb girdle muscular dystrophies	Yes, check *FKRP* gene first. If negative muscle immunohistochemistry will reduce number of candidate proteins	Yes, muscle biopsy required in most cases
Facioscapulohumeral dystrophy	Yes, indirect genetic test available through regional genetics laboratory	Not usually unless genetic test for *FSHD* negative. Inflammatory muscle biopsy may cause difficulty distinguishing from polymyositis
Oculopharyngeal muscular dystrophy	Yes	Not usually
Myotonic dystrophy and PROMM	Yes	Not usually, unless gene tests for MD/PROMM negative
Bethlem myopathy	Not widely available. Consider skin and muscle biopsy. Exclude lamin a/c, emerin and SEPN1	May be helpful for exclusion. May not be definitive
Mitochondrial respiratory chain diseases	Yes (?age associated decline in MtDNA mutation load in blood). *POLG* gene analysis in CPEO	Yes (a) If blood MtDNA analysis negative (b) Muscle needed for mitochondrial enzyme analysis (c) Muscle MtDNA better for MtDNA analysis
Metabolic muscle disorders (glycogenoses, lipidoses)	Yes, but not usually first line	Yes. Also consider specialist metabolic testing, often first line, e.g. non-ischaemic lactate test (glycogenoses) or blood acylcarnitine/urinary organic acids (lipid disorders)

CPEO, chronic progressive external ophthalmoplegia; FKRP, fukutin-related protein; FSHD, facioscapulohumeral dystrophy; MD, mytonic dystrophy; POLG, polymerase gamma; PROMM, proximal myotonic myopathy; SEPN1, selenoprotein 1.

chain reaction (PCR). The importance of the need for an effective treatment has provoked great interest in gene therapy approaches and trials are in progress.

Emery–Dreifuss muscular dystrophy

Emery–Dreifuss muscular dystrophy (EDMD) is a readily recognizable muscular dystrophy which should be considered if contractures are a prominent early clinical feature. Patients present with a scapulohumeroperoneal pattern of muscular weakness and often have strikingly thin muscles. Contractures of the cervical extensor muscles as well as the biceps and long finger flexor tendons are common. Cardiac conduction defects are also frequent and cardiac screening is important.

EDMD is now known to be caused by mutations in genes coding for nuclear envelope proteins emerin and lamin A/C which are located in the membrane surrounding the muscle cell nucleus. Their exact function is uncertain. Emerin causes the X-linked form of EDMD and lamin A/C causes the less common dominant and recessive forms. Accurate genetic diagnosis is critical to provide accurate genetic counselling. Mutations in the lamin A/C gene have also been described in a form of LGMD (LGMD1B; Table 9.33), an autosomal recessive axonal neuropathy and partial lipodystrophy.

Congenital muscular dystrophy

The congenital muscular dystrophies are a genetically heterogeneous group of disorders which present at birth often as floppy infants, who subsequently experience impaired motor and sometimes cognitive development. Kyphoscoliosis is common and varying degrees of brain developmental abnormalities may occur. The degree of CNS involvement tends to determine the overall clinical severity. Patients at the mildest end of the spectrum may present in late teens to the adult neurology muscle clinic with an indolent myopathy, sometimes with contractures.

Nine genes causing CMD have been identified and a classification into five clinical subtypes has been proposed based partly on the underlying molecular defects. In all but one group there is a major defect in the basal lamina or the extracellular matrix of the skeletal muscle fibre. Group 1 patients have a defect in laminin α2. Group 2 patients have defects in glycosylation of α-dystroglycan and some are therefore allelic with LGMD2I caused by *FKRP* mutations (see LGMD section). Group 3 exhibit severe contractures and have defects in extracellular matrix, e.g. collagen type-6, and selenoprotein N (SEPN1). Group 4 have a reduction in integrin α-7 and Group 5 remain uncharacterized.

Table 9.33 Genes/proteins causing limb girdle muscular dystrophies (LGMD).

Type	Chromosome	Protein	Clinical
Autosomal dominant			
LGMD 1A	5q22–q34	Myotilin	Rare, distal legs affected first; slow progression, late CMP in 50%; CK 2–10 × normal
LGMD 1B	1q	Lamin a/c	Rare; proximal legs affected first; slow progression; CMP in 60%; CK 1–2 × normal
LGMD 1C	3p25	Caveolin	Uncommon; variable phenotype: raised CK to progressive proximal weakness, no CMP, CK 3–40 × normal
LGMD 1D	7q	Unknown	Two families; proximal weakness, no CMP, CK 1–3 × normal
LGMD 1E	6q23	Unknown	Single family, proximal weakness, frequent sudden death from CMP; CK 2–4 × normal
LGMD 1F	7q32	Unknown	Single family, proximal weakness, no CMP CK often normal
Autosomal recessive			
LGMD 2A	15q15	Calpain	Uncommon but many different mutations found, very varied phenotype; no CMP, CK 3–80 × normal
LGMD 2B	2p13	Dysferlin	Uncommon with many different muations and variable phenotype (including within family); typically distal weakness; no CMP, CK 10–80 × normal
LGMD 2C	13q	γ-sarcoglycan	Rare, often early onset and loss of walking; respiratory weakness in some, CMP unusual, CK 5–20 × normal
LGMD 2D	17q21	α-sarcoglycan	Rare, variable phenotype but can be early onset, CMP unusual; CK 5–20 × normal
LGMD 2E	4q12	β-sarcoglycan	Rare; typically early onset with severe disability; CMP occasionally; CK 5–20 × normal
LGMD 2F	5q33	δ-sarcoglycan	Rare; early onset with severe disability; proximal weakness; CMP unusual; CK 10–50 × normal
LGMD 2G	17q11	Telethonin	Rare; teenage onset with proximal and distal leg weakness; CMP in 50%; CK 10–30 × normal
LGMD 2H	9q31	TRIM32	Very rare, slow progression; no CMP; CK 2–20 × normal
LGMD 2I	19q13	FKRP	Most common in UK; variable phenotype but respiratory involvement not uncommon and CMP in 30%; CK 4–30 × normal
LGMD 2J	2q31	Titin	Very rare; alleic to Finnish distal myopathy: causes proximal weakness but often relatives with distal weakness
LGMD 2K	9q34	POMT1	Rare; progressive proximal weakness with learning disability and ankle contractures; CK 8–40 × normal
LGMD 2L	11p13	None known	Very rare; CK very raised, no CMP. French–Canadian families, quadriceps and biceps weakness
LGMD 2M	9q31	Fukutin	Very rare; CK very high, infantile onset, proximal and distal weakness legs >arms. May improve with steroids

CK: creatine kinase; CMP: cardiomyopathy; FKRP, fukutin-related protein; POMT, protein O-mannosyltransferase.

Limb girdle muscular dystrophies

There have been many recent gene discoveries in LGMD. An array of proteins with surprisingly different functions has been shown to cause the LGMD phenotype (Table 9.33). Although patients have the common feature of a limb girdle pattern of muscular weakness without facial involvement, clinical differences exist. For example, the propensity to develop cardiomyopathy or respiratory muscle failure varies considerably between different forms. DNA-based diagnosis will allow logical monitoring programmes of cardiac and respiratory function to be developed.

The recessive LGMDs are far more common than the dominant forms. Three of the most common recessive forms for which gene testing is increasingly available are considered in detail.

Calpainopathy – LGMD2A

LGMD caused by calpain mutations typically develops around the age of 15 years with a range of onset between 2 and 40 years. Early milestones are usually normal and pelvic girdle muscle weakness precedes later development of shoulder girdle weakness. On examination, there is typically a scapulohumeralpelvic distribution of weakness. The involvement of periscapular muscles is reminiscent of FSHD but facial involvement is absent or minimal. Muscle atrophy is usually a prominent feature, as opposed to hypertrophy in many other dystrophies (e.g. Becker dystrophy and LGMD21). Particular atrophy of the posterior compartment of the thigh may be a distinguishing clinical feature compared to other LGMDs. Loss of ambulation usually occurs 12–30 years after the onset. Cardiac involvement is not a feature and reduced vital capacity seems to occur only in severe very advanced cases. CK is elevated initially in the course of the disease but not as high as in LGMD2I, dystrophinopathies or LGMD2B.

Dysferlinopathy – LGMD2B

There is a broad phenotypic range associated with mutations in the dysferlin gene. Most simply, there is a proximal LGMD type presentation and a distal presentation (also known as Miyoshi myopathy; see below). In the LGMD presentation, weakness usually begins between 18 and 20 years in a pelvifemoral distribution, often with marked quadriceps involvement. The onset may be relatively abrupt with a very high CK leading to polymyositis as a differential diagnosis. Later, weakness in the arms develops with particular involvement of the biceps. Weakness usually spares the deltoids and also the periscapular muscles so scapula winging is not usual. A degree of lower limb distal involvement affecting gastrocnemius and soleus is not uncommon. Imaging of gastrocnemius may show early changes and may be diagnostically helpful in an otherwise LGMD presentation. Facial and extraocular muscles are spared. Cardiac involvement is not reported.

The other main presentation of dysferlinopathy is with marked lower limb posterior calf compartment weakness, known as Miyoshi myopathy. Patients complain of difficult standing on their tip-toes and over time the weakness spreads to include the limb girdle muscles. A very high CK and sometimes marked infiltrates in the muscle biopsy can cause confusion with myositis but immunohistochemistry using dysferlin antibodies in combination with genetic analysis of the dysferlin gene is usually diagnostic.

Fukutin-related protein dystrophy (LGMD2I)

LGMD2I usually presents between the ages of 11 and 40 years with a mild phenotype but can present with a severe Duchenne-like pattern and degree of weakness. The distribution of muscle involvement is similar, irrespective of the severity with a predilection for axial, neck flexor and the proximal pelvic and shoulder girdle muscles. Facial muscles are usually spared. Scapula winging is common. There may be striking hypertrophy of the tongue, brachioradialis, calves and sometimes the quadriceps. In contrast, there may be atrophy of pectoralis major and deltoid muscles. Prominent lumbar lordosis is common and exercise induced cramping is a frequent complaint. Importantly, one-third of cases develop a dilated cardiomyopathy. Respiratory muscle involvement is also common, manifesting as nocturnal hypoventilation. In contrast to dystrophinopathies, respiratory failure may occur even while the patient remains ambulatory. LGMD2I is caused by mutations in the gene known as the fukutin-related protein (FKRP) which codes for a glycosylation enzyme. Recent data suggest it may be the most common cause of adult onset LGMD identified to date and a single mutation may account for many cases.

Facioscapulohumeral muscular dystrophy

FSHD is an important autosomal dominant disorder frequently encountered in adult specialist muscle practice. Patients commonly have facial muscle weakness as the initial symptom, which may be followed by periscapular and humeral muscle involvement. Later in the disease course lower limb weakness, particularly anterior tibial and abdominal wall weakness may occur. It is notable that the distribution of weakness is often asymmetric, with the right side often being more involved. Isolated periscapular weakness without facial involvement may occur. The severity is variable ranging from isolated asymmetrical scapular winging through to pronounced early onset weakness rendering the patient wheelchair-bound. Scoliosis, deafness and retinal vasculopathy are uncommon additional features.

FSHD is almost fully penetrant by the age of 30 years. It has been known for over 10 years that the gene for FSHD is located on chromosome 4, but identification of the exact gene has remained elusive. Surprisingly, a search of the mapped region did not reveal any genes but did reveal contraction (truncation) of a normally occurring non-coding repeated DNA sequence. The presence of this truncated region of DNA has been shown to associate strongly with chromosome 4 linked FSHD and this is the basis of the available genetic test. It is important to note that this is an indirect genetic test and unlike all the other gene tests described here it is not the gene itself that is being analysed.

Nevertheless, this truncation detection genetic test is a useful aid in the precise diagnosis of FSHD. It is believed that truncation of this region may have a detrimental effect on the true FSHD gene which is suspected to be located elsewhere on chromosome 4, known as the positional variegation effect.

Oculopharyngeal muscular dystrophy

Oculopharyngeal muscular dystrophy (OPMD) is an uncommon disorder characterized by late onset pharyngeal muscle weakness and ophthalmoplegia. It is usually autosomal dominant and highly penetrant although recessive inheritance may occur. OPMD may enter into the differential diagnosis in patients with late onset ophthalmoplegia. The most common genetic defect is an expansion of a short (GCG)7–13 triplet in the poly-A binding protein 2 (*PAB2*) gene on chromosome 14q. Genetic testing for the expanded repeat sequence is available and usually obviates the need for muscle biopsy (Plate 9.10).

Myotonic dystrophy and proximal myotonic myopathy

Myotonic dystrophy (dystrophia myotonica) is an autosomal dominant multi-system disorder ranging in severity from a severe congenital myopathy, which may be fatal, to late onset isolated cataracts. Neuromuscular symptoms in a typical case include facial weakness, mild distal myopathy and myotonia. Variable additional symptoms include cataracts, endocrine disturbance such as diabetes mellitus, cardiomyopathy, hair loss, cognitive slowing, daytime somnolence, bowel dysmotility and respiratory muscle weakness. It is the presence of one or more of these additional features in combination with typical muscle symptoms that usually leads to the correct diagnosis on clinical grounds. However, diagnostic difficulty may arise if the muscular symptoms are not evident or are subtle. For example, we have seen cases presenting initially to diabetic, cardiac, gastrointestinal or memory clinics before full diagnosis.

Genetic anticipation is a prominent feature in myotonic dystrophy. The molecular correlate of anticipation has been shown to be an unstable trinucleotide repeat (CTG) in the 3′ untranslated region of a gene on chromosome 19 called myotonin kinase. Recent evidence suggests that the expanded repeat may exert its toxic effect at the RNA level. There is evidence that the expanded untranslated repeated sequence in RNA forms abnormal degradation resistant nuclear deposits (aggregates). Such nuclear deposits probably impair nuclear matrix function resulting in altered expression of other genes. This effect on other genes may explain the diverse multi-system clinical involvement. For example, there is evidence that expression of the skeletal muscle voltage gated chloride channel is altered in patients with myotonic dystrophy. The resulting chloride channel dysfunction is the probable basis of the myotonia. Mutations in this chloride channel are also the basis of the pure myotonic disorder myotonia congenita.

The diagnosis of myotonic dystrophy is usually straightforward on clinical grounds. DNA-based diagnosis is the initial investigation of choice. A detailed family history will usually reveal other affected members. Genetic counselling should be as for an autosomal dominant disorder with full penetrance but variable expression. It is particularly important to identify females at risk of inheriting the gene in pedigrees. This is because the severe, often lethal, congenital form is confined to the offspring of affected females. Such females can then be offered appropriate genetic counselling and also prenatal diagnosis if they wish.

Patients with myotonic dystrophy should be followed up in a muscle clinic where they can be monitored for systemic complications. There is currently no curative treatment, but the potential now exists to develop drugs which may reduce the abnormal RNA deposition. In most patients myotonia is not symptomatic and does not need treatment. In those cases with symptomatic myotonia we suggest mexiletene is the drug of choice provided the cardiac QT interval is normal.

If the genetic test for MD is negative, consideration should be given to a disorder known as PROMM (proximal myotonic myopathy). This less common disorder is characterized by proximal rather than distal myopathy, but in other respects may exhibit similar features to myotonic dystrophy. Muscle pain may be a prominent feature that may suggest the diagnosis on clinical grounds. The γ-GT concentration may be raised. The genetic defect underlying this autosomal dominant disorder has recently been identified as a CCTG repeat sequence in intron 1 of a zinc finger protein gene on chromosome 3. As in myotonic dystrophy there is evidence that this untranslated defect operates at the RNA level, resulting in nuclear aggregates. Mild anticipation is reported in PROMM families but a severe congenital form has not been described to date (Plate 9.7).

Bethlem myopathy

Bethlem myopathy is an autosomal dominant myopathy caused by mutations in one of three different genes for collagen type 6: COL6A1 and COLA6A2 on chromosome 21q22.3 and COL6A3 on chromosome 2q37. Onset of this so-called 'contractural phenotype' is typically in the first or second decade although occasionally a congenital onset is observed with reduced fetal movements, dislocated hips and arthrogryposis. In childhood there are delayed motor milestones, waddling gait and tripping with falls. There is slow progression in the first decade although there may be stabilization and even transient improvement of muscle strength in the second decade. There is then subsequently slow progression. Life expectancy is usually normal and there is no evidence for cardiorespiratory involvement. Two-thirds of patients require a wheelchair by the age of 50 years. Physical examination shows generalized symmetrical muscle atrophy particularly in the shoulder girdle, upper arms and below the knees. There is general mild weakness with a proximal emphasis. Later there is forearm and neck flexor weakness and also anterior tibial weakness. There is no ophthalmoplegia and facial weakness is rare. Prominent flexion contractures at the interphalangeal joints of the fingers, elbows and ankles are present in most patients and contractures at the metacarpophalangeal joints, shoulders (pectoralis major), tibialis anterior, hamstrings, quadriceps and erector spinae and jaw muscles frequently occur with no relationship between the severity of the weakness and the severity of the contractures. Treatment is supportive.

Muscle biopsy is non-specific. Immunofluorescence of patient fibroblast cultures sometimes shows a reduced expression of collagen type 6 but can be normal. Genetic testing is not widely available. The differential diagnosis includes other myopathies with prominent early contractures including EDMD, autosomal dominant LGMD and rigid spine syndrome with mutations in the selenoprotein N (*SEPN1*) gene and these can be excluded.

Distal myopathies

Distal myopathy is a term that encompasses a variety of genetic and acquired muscle disorders characterized by progressive muscle weakness and wasting beginning in the feet and hands. It is therefore a relatively non-specific category. Most genetic and acquired muscle diseases have a proximal presentation and distal myopathies are uncommon. The clinical classification of a patient into a distal myopathy is helpful because it potentially narrows the differential diagnosis. There are at least 17 primary genetic distal myopathies described in the literature, most of which are very rare. Six of the best characterized entities are outlined in Table 9.34 along with some information about age at onset, muscle biopsy findings and genetics.

When a patient presents with a predominant distal myopathy, in addition to the disorders outlined in Table 9.34, other diagnostic possibilities to consider include FSHD, inclusion body myositis (IBM), myotonic dystrophy, distal hereditary motor neuropathy, central core disease, nemaline myopathy and lipid storage myopathy. Usually in each of these conditions there are associated clinical features (see above and below) which aid the diagnostic process. Although some of the genes for the disorders in Table 9.34 have been identified gene testing is not yet easily available. Exclusion of other conditions by careful clinical evaluation, genetic testing and often muscle biopsy is usually required. Often biopsy of a distal lower limb muscle is more likely to reveal diagnostic pathology. Increasingly, MRI may be used to identify muscle involvement and aid muscle selection for biopsy.

Congenital myopathies

The congenital myopathies are a group of uncommon muscle disorders that were defined on the basis of distinctive morphological muscle biopsy features. Many different disorders are described in the literature. Generally, patients present as floppy infants, sometimes with congenitally dislocated hips, and then usually have delayed motor milestones. The muscle weakness generally follows a fairly indolent course with a benign prognosis. These patients sometimes only first come to attention in the adult muscle clinic. Central core myopathy and nemaline myopathy are of particular note and are described here.

Table 9.34 Summary of the six well-characterized distal myopathies.

Disease	Onset	Weakness	Biopsy	Genes
Welander	>40	Hands	Dystrophic, rimmed vacuoles	AD, 2p13
Miyoshi	>15	Posterior calf	Dystrophic	AR, Dysferlin
Nonaka	>15	Anterior calf	Myopathic, rimmed vacuoles	AR, GNE
Tibial MD	>35	Anterior calf	Dystrophic, rimmed vacuoles	AD, Titin
LODM	>40	Anterior calf	Vacuoles	AD, 2q31
EODM	3–25	Anterior calf	Myopathic	AD, 14q

AD, autosomal dominant; AR, autosomal recessive; EODM, early onset distal myopathy; GNE, glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase; LODM, late onset distal myopathy; MD, muscular dystrophy.

Central core disease

Central core disease (CCD) is an autosomal dominant disorder that presents with neonatal hypotonia. There may be a breech presentation, sometimes with dislocated hips or arthrogryposis. Motor milestones are delayed. There is mild proximal symmetrical muscle weakness and ambulation is usually achieved. Disability is usually mild. Significant cardiorespiratory problems are rare. CCD is associated with an increased risk of malignant hyperthermia (MH). However, the relationship between CCD and MH is complex and only around 30% of CCD patients have MH susceptibility. Most patients with pure MH have histologically normal muscle. Muscle biopsy in CCD typically shows central cores that are devoid of oxidative enzyme and phosphorylase activity. Both MH and CCD are caused by mutations in the ryanodine receptor gene *RYR1*. MH susceptibility testing should be offered to all patients with CCD.

Nemaline myopathy

Nemaline myopathy (NM) is characterized by the presence of rod-shaped structures (nemaline rods) in the muscle fibres. Inheritance can be autosomal dominant or recessive and to date six genetic loci have been described. Three clinical severities are seen: a severe congenital form, the typical congenital form and an adult onset form.

The severe congenital form presents with severe neonatal hypotonia and respiratory insufficiency. Reduced fetal movements are reported *in utero*. Occasionally there may be severe arthrogryposis and dilated cardiomyopathy. Early mortality because of respiratory complications is common. Occasional long-term survival with respiratory support has been described accompanied by major motor weakness and inability to ambulate. The typical congenital form presents with neonatal hypotonia with less respiratory difficulty. Weakness is milder and although motor milestones are delayed independent ambulation is achieved and most patients have an independent life.

The adult onset form presents between the ages of 20 and 50 years. Myalgia may be predominant with moderate proximal weakness which is usually slowly progressive. Facial muscle weakness and neck flexion weakness are common in all forms. The face is often elongated with a tent-shaped mouth and a high arch palate. The degree of the facial abnormality correlates with the overall severity of the condition. Some adult cases have been described with more rapidly progressive weakness. Respiratory involvement is rare but can occur; nemaline myopathy should always be considered in the adult presenting with unexplained respiratory muscle weakness. All the known NM genes identified encode components of the sarcomeric thin filaments. In AD NM mutations in α and β tropomyosin are found and in recessive NM nebulin, NEM1, NEM2 and troponin-1 mutations are described. Mutations in α-actin and ACTA1 may cause either dominant or recessive disease.

Skeletal muscle channelopathies

Periodic paralyses and myotonias

Periodic paralysis and inherited myotonia were the first human disorders in which genetic dysfunction of ion channel genes was identified. They are conditions in which there is a disturbance in skeletal muscle fibre membrane excitability. The periodic paralyses are autosomal dominant disorders in which patients experience focal or generalized episodes of muscle weakness of variable duration. They have been characterized on the basis of the change in serum potassium during an attack. In hyperkalaemic periodic paralysis potassium triggers an attack which will be ameliorated by glucose ingestion. In contrast, patients with hypokalaemic paralysis will notice improvement with potassium ingestion but worsening with glucose. The classification based upon potassium is useful clinically although a genetic classification has now emerged (Table 9.35). Mutations in one of three skeletal muscle ion channels genes associate with human periodic paralysis. These are the voltage gated sodium and calcium channel genes *SCN4A* and *CACNA1S* and the voltage-independent potassium channel gene *KCNJ2*. All forms of periodic paralysis share the common feature that during an attack the muscle fibre membrane becomes electrically inexcitable but the mechanisms leading to this state vary and are described below.

Myotonia is a clinical disorder in which patients experience muscle stiffness because of a failure of normal electrical inactivation of activated muscle. Myotonia may result from genetic mutations in either the muscle voltage gated chloride channel *CLCN1* (dominant or recessive myotonia congenita) or the voltage gated sodium channel *SCN4A* (dominant paramyotonia congenita).

Hyperkalaemic periodic paralysis and myotonias caused by skeletal muscle sodium channel dysfunction

In hyperkalaemic periodic paralysis (hyperPP) patients typically experience recurrent attacks of muscle weakness starting in the first decade of life. Precipitants include rest following exercise, cold, potassium ingestion or stress. Attacks may vary in severity from mild weakness to total paralysis. The duration of attacks is usually less than 2 hours. Typically, the attack frequency declines with age but patients often develop a fixed myopathy of variable severity. Muscle biopsy in such cases often reveals tubular aggregates and or a vacuolar change. In humans, unlike equine forms, death is extremely rare in hyperPP or hypoPP. Cardiac arrhythmias are also uncommon except in Andersen's syndrome (see below).

HyperPP is caused by 'gain of function' point mutations in the muscle sodium channel *SCN4A*. Sodium channel α-subunit mutations (*SCN4A*) lead to defective fast inactivation of the skeletal muscle Na^+ channel. The resulting persisting inward sodium current (a gain of function) impairs repolarization and increases membrane excitability. Depending on the degree of increased membrane excitability, a patient may experience myotonia or paralysis. It is notable that similar gain of function mutations in a neuronal sodium channel gene *SCN1A* result in increased neuronal excitability and associate with a form of epilepsy (see

Table 9.35 Skeletal muscle channelopathies: a genetic classification.

Gene	Channel	Disease	Inheritance
*CACNA1S**	Calcium channel	HypoPP1	AD
	L-type calcium α-subunit	MH	AD
*SCN4A**	Sodium channel	HyperPP	AD
	Nav1.4 α-subunit	PMC	AD
		PAM	AD
		HypoPP2	AD
*KCNJ2**	Potassium channel, K_{ir}2.1	Andersen's syndrome	AD
*CLCN1**	Chloride channel, ClC1	Myotonia congenita	AD/AR
		MD1, MD2†	AD
RYR1	Ryanodine receptor	MH	AD
	Calcium release channel	Central core disease	AD¶ AR

AD, autosomal dominant; AR, autosomal recessive; ClC1, chloride channel 1 gene/channel; Hyper PP, hyperkalaemic periodic paralysis; HypoPP, hypokalaemic periodic paralysis; K_{ir}2.1, potassium inward rectifier; MH, malignant hyperthermia; PAM, potassium aggravated myotonia; PMC, paramyotonia congenita.

* DNA-based diagnosis available in UK.

† Altered splicing of *CLCN1* has been shown in both forms of myotonic dystrophy (MD) as the basis of the myotonia.

¶ Gain of function.

below), thus representing a direct pathophysiological parallel between muscle and brain sodium channel diseases.

Many attacks are brief and do not require treatment. If necessary, acute attacks can be terminated by ingestion of carbohydrate or inhaled salbutamol. Preventative treatment with acetazolamide or a thiazide diuretic may be required. It remains unproven if reducing attack frequency with such agents reduces the likelihood of the subsequent development of myopathy.

Paramyotonia congenita (PMC) is a form of myotonia that appears during exercise and worsens with continued activity. EMG at rest often shows some myotonia. Low temperature often precipitates symptoms in these patients and cooling produces repetitive spontaneous motor unit discharges with a decrement in the muscle action potential amplitude. PMC is also caused by mutations in the voltage gated skeletal muscle sodium channel α-subunit (*SCN4A*) and PMC is therefore allelic with hyperPP. PMC is inherited as a highly penetrant autosomal dominant trait. Mutations have been found throughout the gene, although exon 24 appears to be a hotspot for mutations. PMC associated point mutations confer a gain of function. However, the resulting impairment of fast inactivation is less than that associated with mutations associated with hyperPP. Mexiletene is an effective symptomatic treatment for PMC. Milder forms of myotonia without cold sensitivity are also described in association with different sodium channel point mutations, known as potassium aggravated myotonia.

Hypokalaemic periodic paralysis – a muscle calcium or sodium channel disorder

Hypokalaemic periodic paralysis (hypoPP) is autosomal dominant with de novo dominant mutations accounting for one-third of cases. Attacks are precipitated by a period of exercise followed by rest or by carbohydrate loading. Attacks typically develop in the early hours of the morning and may last hours to days. Serum potassium is typically low at the onset but may normalize quickly. Attack frequency tends to decline with age but a fixed myopathy may develop. Myotonia does not occur in hypoPP.

Point mutations in two separate muscle channel genes may cause hypoPP. The majority of cases harbour one of three point mutations in the L-type calcium channel, *CACNA1S* – also known as hypoPP type 1. Far less frequent mutations have been described in the muscle sodium channel *SCN4A* (known as hypoPP-type 2).

Mutations in the L-type calcium channel α_1-subunit (dihydropyridine receptor; *CACNA1S*) account for about 70% of cases of hypoPP. All mutations are arginine substitutions in the voltage sensor (S4) of the channel protein. It remains unclear how mutations in *CACNA1S*, which does not have a major role in determining muscle membrane excitability, result in paralysis but experimental studies indicate that loss of the normal function of the channel is necessary for the attacks.

HypoPP associated with *CACNA1S* mutations exhibits reduced penetrance in females (50%) compared to complete penetrance in males. Specific mutations appear to have discrete clinical features, e.g. R528H is common, with later onset and associated myalgias.

HypoPP can also be caused by missense loss of function mutations in the voltage sensor of domain 2 of *SCN4A* but these are uncommon in the UK. There is some evidence that such hypoPP cases may experience worsening of attacks with prominent myalgia when exposed to acetazolamide. In this setting an alternative carbonic anhydrase inhibitor dichlorfenamide seems to be effective.

In summary, current evidence indicates that hyperPP is a gain of function disorder caused by *SCN4A* point mutations. In contrast, hypoPP associates with loss of function mutations in either *CACNA1S* or in *SCN4A*. It remains unclear how loss of function mutations result in the partially depolarized inexcitable state that occurs in hypoPP.

Periodic paralysis and cardiac arrhythmias – a skeletal muscle potassium channel disorder

Most cases of periodic paralysis do not associate with cardiac arrhythmias because the responsible channel (*CACNA1S*, *SCN4A*) is not expressed in cardiac muscle. Andersen–Tawil syndrome is a form of dyskalaemic periodic paralysis in which cardiac involvement is frequent (the resting ECG commonly shows bigeminy). In addition to periodic paralysis, patients may have atrial and/or ventricular arrhythmias and may also have characteristic facial and skeletal features (Plate 9.8). From a practical point of view, this disorder should be considered in any case of periodic paralysis with arrhythmia.

Andersen's syndrome is caused by mutations in a potassium channel termed Kir2.1. This inward rectifying potassium channel Kir2.1 is encoded by *KCNJ2* on chromosome 17q23. The functional channel is a homotetramer important for cardiac and skeletal muscle membrane hyperpolarization and also has a role in skeletal bone precursor cell migration and fusion during development. There is intrafamilial variability and partial manifestation of the phenotype is common. During an attack, serum potassium is most commonly low but may be normal or high. In patients with hypokalaemia, oral potassium supplements may improve the weakness. In some families, increasing plasma potassium concentration with acetazolamide improves arrhythmias at the expense of exacerbating weakness. Once the diagnosis is made detailed cardiac assessment is needed. However, the optimum management to prevent malignant arrhythmias is not certain.

Myotonia congenita – a skeletal muscle chloride channel disorder

Dominant (Thomsen's disease) and recessive (Becker's disease) forms of myotonia congenita are recognized. Patients experience differing degrees of muscle stiffness and muscle hypertrophy. The dominant form is less common and generally milder. Patients present with muscle stiffness because of impaired voluntary muscle relaxation. Patients describe marked muscle stiffness at the onset of activity, but the more they continue the less stiff the muscles become – the so-called 'warm-up phenomenon'. While

90% show myotonia on EMG, only 50% have percussion myotonia on examination. There is usually normal power at rest, although a minority have proximal weakness. Muscle hypertrophy and myalgia may occur in both forms but are more prominent in the more common recessive form of the disease. Electrophysiologically, *in vivo* myotonia (and paramyotonia) is characterized by uncontrolled repetitive action potentials at the sarcolemma initiated by a voluntary activation. This persistent involuntary activation prevents the patient from relaxing the muscle, hence the complaint of muscle stiffness and limitation of free flowing movements.

Both forms of myotonia congenita are caused by mutations in a muscle voltage gated chloride channel (*CLCN1*) located on chromosome 7q35.10. There is evidence that, unlike all other voltage gated ion channels, this channel has two separate ion pores through which chloride ion passage may occur. The resting membrane potential in skeletal muscle is mainly dependent upon the chloride channel conductance; *CLCN1* mutations result in impaired chloride conductance and so produce partial depolarization of the membrane. This creates the electrophysiological condition of increased excitability and repetitive firing after muscle activation, necessary for myotonia to occur.

Metabolic muscle disease

Mitochondrial respiratory chain diseases

A bewildering array of clinical phenotypes may associate with dysfunction of the mitochondrial respiratory chain. The respiratory chain is critical for aerobic ATP production and it is therefore perhaps unsurprising that virtually any body tissue can be affected. Tissues such as skeletal muscle and brain, with a high dependence on ATP, are commonly affected. The clinical manifestations of skeletal myopathy varies and can include: progressive external ophthalmopleagia, isolated proximal myopathy or, less commonly, distal myopathy (Plate 9.9). Exercise intolerance is a frequent accompaniment to limb myopathy and rhabdomyolysis is an infrequent but recognized complication. Myopathy may occur in isolation or in combination with a more complex phenotype which may involve the CNS. Examples of classic CNS mitochondrial disease include mitochondrial encephaolomyopathy with lactic acidosis and strokes (MELAS) and mitochondrial encepahlomyopathy with ragged red fibres (MERRF; Plate 9.9). Although the typical mitochondrial syndromes in their fully developed form can usually be recognized by the experienced neurologist, there is a wide variety of clinical presentations and mitochondrial disease may frequently enter the differential diagnosis in patients with complex CNS disorders, especially if limb weakness is present.

A combination of genetic and muscle histochemical and biochemical investigations can usually result in an accurate diagnosis. Muscle biopsy remains an extremely important investigation in patients suspected to have mitochondrial disease. The hallmark muscle biopsy finding of the ragged red fibres on the Gomori trichrome stain is diagnostic in many, but not all, patients with mitochondrial respiratory chain disease.

Mitochondrial respiratory chain disease may be more common than previously considered. One study indicated possibly 10/100,000 in the UK population. Although most adult patients with mitochondrial disease harbour mutations in mitochondrial DNA, mutations in nuclear encoded genes can cause respiratory chain dysfunction resulting in neurological illness. To date, most of the nuclear genes identified cause mitochondrial respiratory chain disease with a neonatal or early childhood onset. However, recently mutations in the nuclear gene for mitochondrial polymerase gamma (*POLG*) have been found in adults presenting with one of a number of phenotypes that the adult neurologist is more likely to encounter.

It is evident that all forms of inheritance (autosomal dominant, autosomal recessive, X-linked, maternal and sporadic) are possible in mitochondrial respiratory chain disease depending on the genetic basis. The majority of adult mitochondrial phenotypes associate with primary mutations in mitochondrial DNA (MtDNA) (Table 9.36). These include large-scale rearrangements

Table 9.36 Classification of mitochondrial respiratory chain diseases.

Defects in MtDNA	
Mutations in protein coding genes	**Phenotype**
e.g. Mitochondrial ND genes	LHON MELAS
Mutations in ATPase genes	NARP Leigh's disease
Mutations in protein synthesis genes	
tRNA genes	CPEO Myopathy MELAS MERRF
rRNA genes	Deafness
Defects in nuclear genes	
Defects in intergenomic signalling	
POLG	AD CPEO AR CPEO MERRF/MELAS
Defects in MT resp. chain assembly	
SURF-1	Leigh's disease
Defects in resp. chain subunit genes	
Complex I, II, III or IV	Encephalomyopathies
Defects in mitochondrial motility	AD optic atrophy

AD, autosomal dominant; AR, autosomal recessive; CPEO, chronic progressive external ophthalmoplegia; LHON, Leber's hereditary optic neuropathy; MERFF, myoclonic epilepsy with ragged red fibres; MELAS, mitochondrial encephaolomyopathy, lactic acidosis, strokes; MT, mitochondria; NARP, neuropathy, ataxia, retinitis pigmentosa; ND, northern dot; POLG, polymerase gamma.

Table 9.37 Common mitochondrial phenotypes in adults.

Phenotype	Genetics	Inheritance
CPEO	Deletion in mtDNA	Sporadic
	Multiple deletions	AR/AD
	MtDNA point mutations	Maternal
Myopathy	Deletion mtDNA	Sporadic
	MtDNA point mutations	Sporadic or maternal
MELAS	MtDNA point mutation (A3243G)	Maternal
MERRF	MtDNA point mutation (A8344G)	Maternal
LHON	MtDNA point mutation (11778)	Maternal

AD, autosomal dominant; AR, autosomal recessive; CPEO, chronic progressive external ophthalmoplegia; LHON, Leber's hereditary optic neuropathy; MELAS, myoclonic epilepsy with lactic acidosis, strokes; MERRF, mitochondrial encephalopathy with ragged red fibres.

(such as deletions) which are only infrequently passed on to the succeeding generation. In contrast, the other common mutations in MtDNA, point mutations, are usually passed down the maternal line. Unfortunately, the factors that determine the amount of a particular point mutation that may be passed down cannot be predicted with accuracy. Thus, it is extremely difficult to offer women who harbour disease-causing point mutations accurate recurrence risks. Until current research efforts identify the factors that influence the recurrence risks for such women, the only definite way to avoid maternal transmission is to consider ovum donation.

A mitochondrial respiratory chain disease may be suspected in a number of clinical settings and it is generally helpful to consider splitting up defined phenotypes (Table 9.37), although in practice there is considerable clinical overlap.

Typical phenotypes that predominantly involve skeletal muscle include isolated myopathy, chronic progressive ophthalmoplegia and the Kearns–Sayre syndrome. Typical phenotypes that include a combination of myopathy with prominent CNS involvement include MELAS and MERRF.

Isolated mitochondrial myopathy

Isolated chronic progressive external ophthalmoplegia (CPEO) and Kearns–Sayre syndrome are common manifestations of mitochondrial disease. Onset may be before 20 or after 50 years in most cases. There is a slow evolution of symmetrical extraocular muscle weakness and diplopia is uncommon. Ptosis progresses over time and measures to raise the eyelids may be required such as eyelid props or sometimes eyelid surgery. A single clonal deletion of mtDNA is the most common genetic defect in patients with CPEO, although point mutations in tRNA genes and multiple deletions of mtDNA may be the cause.

Kearns–Sayre syndrome is defined by the triad of progressive external ophthalmoplegia (PEO), pigmentary retinopathy and onset before the age of 20 years, with at least one of the following: high CSF protein >100 mg/dL, cerebellar ataxia or cardiac conduction block. It is most commonly caused by single large deletions in mtDNA but has a far more serious prognosis compared to isolated CPEO. Patients often have a progressive limb myopathy and frequently require a pacemaker for AV block. Patients with later onset nearer to 20 years may have a milder prognosis.

Autosomal dominant/recessive progressive external ophthalmoplegia (PEO) with multiple deletions

AD/AR progressive external ophthalmoplegia is an adult onset condition caused by nuclear genes that affect mtDNA maintenance resulting in multiple deletions of mtDNA. In addition to PEO there may be a variety of clinical features including peripheral neuropathy, ataxia, tremor, parkinsonism, depression, cataracts, pigmentary retinopathy, deafness, rhabdomyolysis and hypogonadism. A particular variant of multiple deletion PEO is the syndrome of mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is characterized by PEO and marked gastrointestinal malfunction and cachexia. There is also a multiple deletion PEO variant in which there is dramatic sensory ataxic neuropathy termed SANDO (sensory ataxic neuropathy dysarthria and ophthalmoplegia). A number of different nuclear genes have been implicated in these different multiple deletions disorders and one of the most common is the gene encoding the mitochondrial DNA polymerase gamma (*POLG1*).

MELAS

MELAS is a serious stroke syndrome that most commonly associates with point mutations in mtDNA transfer RNA genes. The most common is the A3243G mutation in the tRNA gene for leucine (*UUR*) accounting for around 80% of MELAS cases. The stroke-like episodes are often dramatic and are different from typical ischaemic strokes in that the patients are encephalopathic. Typically, episodes begin with severe 'migraine-like' headache with nausea and vomiting. There may be focal or generalized seizures in an episode followed by hemipareis, hemianopia or cortical blindness. The strokes are often parieto-occiptial and do not conform to vascular territories. Patients often experience multiple stroke-like episodes. Dementia, ataxia, deafness, muscle weakness, cardiomyopathy and diabetes are frequent accompaniments. Treatment of acute episodes is supportive.

MERRF

MERRF patients experience myoclonus, epileptic seizures, ataxia and muscle weakness. Onset is usually in childhood but adult onset is described. Myoclonus is stimulus sensitive and the seizures may be tonic–clonic and there is often photosensitivity. There is a common lysine tRNA gene mutation associated with MERRF. In addition to myopathy, approximately one-third of MERRF cases have significant cardiomyopathy.

In practice, the mitochondrial disease needs to be considered when there may only be fragments of full clinical syndromes or the patients have elements of a number of different syndromes. Useful pointers to consider in patients with CNS syndromes that might suggest a mitochondrial aetiology are the presence of myopathy, neuropathy or deafness in the context of a complex CNS phenotype.

Treatment and support for patients with mitochondrial disease

Patients with confirmed mitochondrial disease require support in a multidisciplinary clinical team setting. Often this is lead by a neurologist and a therapist with close links to a range of different disciplines as required such as physiotherapy, occupational therapy, cardiology, endocrinology/diabetes, audiology and speech therapy. Although a number of medications/vitamins have been suggested there is little in the way of convincing trial data to support their use. However, some data exist in support of coenzyme Q10 which we offer to all patients with mitchondrial respiratory chain diseases.

Diagnostic strategy in suspected mitochondrial disease

In practice, if a mitochondrial respiratory chain disease is suspected it is sensible to select the available mtDNA point mutations (3243, 8344 and 8993) to be analysed in a blood sample. The hit rate from this limited analysis of blood mtDNA is likely to be low. However, if positive, a secure diagnosis of mitochondrial disease is achieved without the need for further investigations. In CPEO patients *POLG* gene mutation analysis is possible. In patients with Leber's hereditary optic neuropathy (LHON) the majority of cases will have a mutation at 11778, 14484 or 3460 and the hit rate for leucocyte DNA testing much better. In a non-LHON patient if no mutation is detected in blood the gold standard investigations include muscle biopsy and respiratory chain enzymology. The majority of patients with a mitochondrial DNA mutation will have ragged red fibres and/or cytochrome C oxidase negative fibres and/or a measurable defect on mitochondrial respiratory chain enzymology. Furthermore, muscle tissue is a much better tissue to analyse for mtDNA mutations, in particular mtDNA deletions are more reliably detectable. If the above assessments do not produce a positive result and an mtDNA mitochondrial disease is suspected, total sequence analysis on muscle mtDNA can be undertaken and is increasingly available in specialist centres.

Glycogenoses and lipid storage disorders

In addition to mitochondrial respiratory chain disorders the other metabolic disorders in muscle include defects in glucose metabolism (glycogen storage disorders) and defects in fat metabolism (lipid storage disorders). Patients with these autosomal recessive disorders generally develop muscle pain on exertion. Myoglobinuria and sometimes fulminant rhabdomyolysis may occur. Patients with McArdle's disease (the most common glycogenosis caused by myophosphorylase deficiency) present with muscle pain soon after commencing exercise. The pain can be severe and cramping, often causing the patient to stop. A second wind phenomenon is common. The forearm non-ischaemic lactate test will show a blunting of the expected rise in muscle lactate induced by repeated isometric exercise because of a failure to breakdown glycogen. Muscle biopsy will allow histioenzymatic staining for myophosphorylase, absent in McArdle's disease. Genetic testing is available but is usually performed after the metabolic defect has been confirmed.

Of the many disorders of lipid metabolism, the most common lipid storage disorder is carnitine palmitoyl transferase-II (CPT-II) deficiency. Adults with CPT-II deficiency usually present with muscle pain induced by prolonged exercise, and often the pain may not develop until some time after exercise. Post-exercise myoglobinuria is frequent. Rhabdomyolysis is more likely to occur after fasting or if there is intercurrent infection or dehydration. Hypoketotic hypoglycaemia may occur. Occasionally, patients with CPT-II deficiency present with a painless proximal myopathy. Muscle biopsy light microscopy may reveal abnormal accumulations of lipid. Muscle tissue can be used for specific enzyme assays. The pattern of acylcarnitines in blood is particularly useful whenever a lipid storage disorder is being considered. Molecular genetic diagnosis is available.

Conclusions

The diagnosis of patients with genetic muscle disorders has truly entered the molecular genetic era. DNA-based diagnosis is now available for many of these disorders and often removes the need for invasive tests such as muscle or nerve biopsy. Efficient selection of genetic tests is important and neurophysiology has a particularly important role in this regard for genetic muscle channelopathies. Muscle biopsy remains essential in certain situations, e.g. in the comprehensive investigation of patients with LGMD and in some metabolic myopathies. It is worth noting that while a blood sample is all that is required for testing in nuclear gene disorders, muscle tissue remains most useful for mitochondrial DNA analysis. In our view, all clinical neurologists need to be aware that a wealth of genetic diagnostic possibilities exists for these patients, and that achieving such diagnostic precision on a routine basis is important. Often, this will involve referral to a specialist muscle service.

Acquired muscle diseases

Inflammatory myopathies

The inflammatory myopathies are diseases whose primary pathology is of inflammation within muscle. This definition thus excludes those genetic muscle disorders discussed above in which inflammatory change may occur (e.g. dystrophinopathy, FSHD or dysferlinopathy), and also diseases in which inflammation affects associated structures rather than muscle itself, as in polymyalgia rheumatica. The inflammatory myopathies can be divided into four principal classes on the basis of their aetiology (Table 9.38). Their diagnosis can be further refined by distinctive clinical and pathological features that reflect differing fundamental causes and processes, although at present the latter are incompletely understood.

Idiopathic inflammatory myopathies

These are the most commonly encountered acquired muscle diseases and their discussion forms the framework for the remaining conditions. Three subtypes exist:

Table 9.38 The inflammatory myopathies.

Idiopathic	
Dermatomyositis, polymyositis, inclusion body myositis	
Associated with connective tissue disease	
SLE, rheumatoid arthritis, mixed connective tissue disease, Sjögren's disease	
Infective/post-infective	
Viral (HIV, EBV, CMV, HTLV-1), bacterial (staphylococcal, Lyme, tuberculosis), parasitic (nematodes, cestodes, protozoa)	
Miscellaneous	
Vasculitic, non-infective granulomatous (e.g. sarcoid), eosinophilic syndromes	

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HTLV, human T-lymphocyte virus; SLE, systemic lupus erythematosus.

1 *Dermatomyositis* (DM) in which the inflammatory process also, but not necessarily, involves the skin.
2 *Polymyositis* (PM): isolated inflammation of the muscles (but similar findings may occur in association with several rheumatological diseases; see below).
3 *Inclusion body myositis* (IBM) which has a distinctive clinical pattern with less, if any, inflammatory change on biopsy.

All three share the key features of proximal lower limb wasting and weakness as the main clinical findings. However, they may be distinguished by specific features of their clinical presentation and the findings on investigation. All are caused by separate pathological mechanisms. However, distinguishing one from another, or indeed from other conditions, can be difficult. There remains both incomplete understanding of their aetiology and a dearth of evidence on which to base decisions about their treatment.

Dermatomyositis

Dermatomyositis is the inflammation of muscle and skin. Epidemiological data are imprecise, but DM is uncommon, with an incidence of approximately 1/100,000. Unlike the other idiopathic inflammatory myopathies, children can be affected and it is by far the most common such condition in that age group. DM is more common in non-Caucasians and in women.

DM is a humorally mediated autoimmune disorder, in which the pathology is that of a microvasculopathy (Plate 9.10a). Activated complement is found deposited in muscle capillaries and other tissues, which directs subsequent cellular inflammation. The trigger to this is unknown but postulated mechanisms include deposition of circulating immune complexes or a response to an as yet unknown endothelial antigen.

Clinically, DM typically produces a subacute, progressive, proximal and symmetrical weakness, affecting the lower limbs more than the arms. Rarely does the condition lead to pronounced distal weakness. CK is usually raised (see below). There is often some myalgia, but not severe pain. The extraocular and facial muscles are typically spared, but dysphagia may be a problem in severe or advanced cases, while neuromuscular respiratory compromise is also well recognized. A more explosive presentation can occur, even leading to overt myoglobinuria.

The skin manifestations of DM usually precede the myopathy, but they may be difficult to detect if they are not specifically looked for, particularly in people with dark skin. The classic dermatological presentations are the 'heliotrope' erythematous rash of the face (especially the eyelids) and upper trunk. This rash is photosensitive, and often occurs with some oedema and telangiectasia. The hands can typically demonstrate Gottron papules, thickening over the surfaces of the knuckles, but may also show either a more subtle general coarseness of the skin ('mechanic's hands') or nail bed capillary change.

Some patients have the skin changes only without clinical weakness or any elevation of CK, leading to the diagnostic term 'dermatomyositis sine myositis'. Muscle biopsy in these cases usually demonstrates the abnormalities seen in DM. In such amyopathic patients, the condition may resolve without need for immunosuppressive treatment, although recent work identified a high incidence of interstitial lung complications. Finally, typical DM over time may lead to calcinosis within affected tissues. Calcinosis can be quite marked and produces striking changes on imaging. Early treatment is thought beneficial in minimizing this last complication.

Other systems may also be involved, notably the lungs and the heart. Approximately 20% of patients demonstrate evidence of an interstitial lung disease which can rarely be the first symptom. The most common symptoms are of cough and dyspnoea, typically with bibasal crepitations on auscultation of the chest. Lung complications are most commonly slowly progressive but symptoms can develop acutely. Twenty five per cent of those patients with abnormal pulmonary investigations remain asymptomatic. Pulmonary complications are associated with Jo-1 (anti-tRNA synthetase) IgG antibodies. These are present in 20% of DM cases of whom 70% have evidence of interstitial lung disease. The lung pathology is variable, but only bronchiolitis obliterans is likely to respond to immunosuppression. Early treatment, aiming to prevent permanent pathological muscle change, also prevents severe long-term pulmonary disease.

The exact incidence of cardiac involvement in idiopathic myositis is uncertain but several studies found congestive heart failure and ischaemia to be more common than in controls. Up to 50% of cases in some series have ECG evidence of dysrhythmias, conduction block or ischaemic change pointing to a high incidence of subclinical cardiac involvement. Case reports have identified similar inflammatory change in both the myocardium and conducting system to that found in skeletal muscle.

Large series of cases of DM find an approximate 20% association with malignancy, most commonly with adenocarcinoma and gynaecological tumours. Those most at risk are older, female and non-Caucasian patients. A thorough clinically directed approach to detecting an underlying malignancy is therefore indicated, with careful history-taking and examination for undisclosed symptoms or signs (e.g. weight loss, post-menopausal bleeding, breast lump or rectal mass). Appropriate further examination with imaging and/or specialist review may be necessary.

The prognosis of DM is worse in those with pulmonary or cardiac complications, underlying malignancy, arthritis, hypergammaglobulinaemia or in acute or febrile presentations.

Polymyositis

Polymyositis is characterized by a progressive, proximal and symmetrical weakness without the skin lesions seen in DM. It is probably of similar or slightly lower incidence and prevalence to DM. It is very rare in those under 20, and is typically a disease of middle or later life. The course of PM is variable but is somewhat slower to evolve than DM. Although it can be rapidly progressive, the most frequent presentation is with progressive weakness, in which the exact onset is difficult to pinpoint and symptoms progress over months. Myalgia is typical but rarely severe. As with DM, distal and facial weakness is rare but respiratory muscle involvement can occur and can be life-threatening; it is most often seen when the disease is rapidly worsening.

Polymyositis differs fundamentally from DM in being a cell-mediated disease. CD8-positive T lymphocytes respond to an unknown muscle antigen by invading and destroying non-necrotic muscle fibres that express major histocompatibility complex protein (MHC-1; Plate 9.10b). Unlike DM, blood vessels are spared. Respiratory and cardiac complications can develop at similar rates as occur in DM. Polymyositis also shares with DM the particular association of interstitial lung disease with antisynthetase antibodies.

Because PM presents with an absence of helpful associated clinical signs such as the skin involvement of DM or the particular pattern of weakness of typical IBM, 'pure' PM can be diagnosed in error. At the clinically milder end of the spectrum, care must be taken not to over-interpret pain or submaximal effort on examination. At the other, PM must be distinguished from other conditions that can provoke a raised CK and inflammatory changes on biopsy. All the clinical and investigation findings must be considered together and an open mind kept to the need to review or revise a diagnosis over time. In particular, 'failure' to respond to immunosuppressants should raise the possibility that a dystrophic process is, in fact, the cause.

Inclusion body myositis

Sporadic inclusion body myositis occurs somewhat more frequently than DM or PM and is probably the most prevalent acquired myopathy. Unlike either PM or DM it appears to be most commonly a disease of Caucasian men. Other racial groups seem less frequently affected and the male to female ratio is 3 : 2. Typically, IBM occurs late in life and onset before age 30 years is highly unusual. Rare hereditary forms of IBM exist with either autosomal recessive or dominant patterns of inheritance.

The onset of IBM is insidious and usually slower than seen with PM or DM. Classically, IBM causes a distinctive pattern of wasting and weakness involving the quadriceps and deep finger flexors (Plate 9.11). This compromises the most crucial functions of the upper and lower limbs, hand grip and maintaining upright posture; falls may occur relatively early, because of buckling of the knees. Dysphagia occurs in 10–30%. Ankle dorsiflexion weakness can also occur, and these distal signs, plus occasional mild facial involvement and a frequently asymmetrical pattern of weakness allow clinical distinction to be made from other conditions.

The aetiology of IBM is uncertain. Whether it is a degenerative process and whether any endomysial inflammatory component (which may be substantial) is merely a secondary process is still debated. Support for it being degenerative comes from both the finding of amyloid material in the almost pathognomic cellular inclusions and rimmed vacuoles seen on biopsy (Plate 9.10c), and the failure of IBM to respond to all immunosuppressant medications in controlled trials.

There appears to be no link to malignancy. Antisynthetase antibodies are less frequently associated than with DM or PM, and pulmonary or cardiac complications are unusual.

Investigation of inflammatory myopathy

Serum creatine kinase levels

The level of serum CK is raised in all three conditions and offers some guide to the degree of inflammation. It may be raised up to 50 times normal in severe PM and DM; the typical rise in IBM is typically less than 10-fold. It is very important to note that definite deterioration can occur without an accompanying rise in CK, especially of DM. It should also be borne in mind that quoted 'normal' values of CK can be misleadingly low as there is considerable variation in CK levels across a normal population. As such, diagnosis of 'pure PM' should not be made solely on a borderline elevation in CK levels.

Neurophysiology

Typical myopathic features are common in myositis, while frequent fibrillation and spontaneous repetitive discharges can be indicative of active inflammation. A useful rule of thumb from highly experienced practitioners is that when EMG is performed to confirm myopathy, seemingly normal findings frequently turn out to be IBM.

Muscle biopsy

Muscle biopsy is the keystone of diagnosis. It should be considered and if at all possible performed in every case before treatment is initiated. The idiopathic inflammatory myopathies share some pathological features but aspects of the pathology of each may be diagnostic (Table 9.39; Plate 9.10). Typical changes are not always present, however, and thus interpretation can be difficult. The clinical and pathological findings need to be interpreted in conjunction to make the correct diagnosis.

Table 9.39 Characteristic pathological findings of the idiopathic inflammatory myopathies.

Condition	Muscle fibres	Blood vessels
DM	Focal infarctions; perifascicular atrophy	Capillary necrosis and undulating tubules or other endothelial abnormalities; deposition of immunoglobulin and activated complement membrane attack complex
PM	Partial invasion of non-necrotic fibres by activated CD8 lymphocytes and macrophages (seen less in IBM and not in DM). Uniform expression of class I MHC products on surface of all fibres	Rarely involved: possible secondary capillary necrosis
IBM	Rimmed vacuoles; inclusions staining for ubiquitin and amyloid; 15–18 nm tubular filaments in nucleus or cytoplasm (may require extensive EM)	Can be normal; possible increased capillarity

DM, dermatomyositis; EM: electron microscopy; IBM, inclusion body myositis; MHC: major histocompatibility complex; PM, polymyositis.

Extended investigation of inflammatory neuropathies

- *Lung:* a chest radiograph may identify bibasal shadowing. Chest radiography is insensitive, being normal in 10% of those with proven lung involvement. High-resolution CT scanning is more sensitive, characteristically revealing linear opacities and a 'ground glass' appearance of the lung bases. Pulmonary function tests are also indicated; a restrictive pattern with reduced lung volumes and decreased diffusing capacity for carbon monoxide is typical.
- *Heart:* an ECG is indicated in all patients. Clinical evidence of cardiac involvement necessitates further assessment with 24-hour Holter recording, echocardiography and review by a cardiologist.

Treatment of idiopathic inflammatory myopathies

The treatment of idiopathic inflammatory neuropathies is based largely on expert opinion rather than any evidence. Indeed, the Cochrane collaboration's systematic review on the treatment of DM and PM concluded that, 'the small number of randomized trials of immunosuppressants and immunomodulatory therapies are inadequate to decide whether these agents are beneficial'. Guidelines for management are open to the influences of personal practice, but one suggested approach is given in Table 9.40.

For IBM no beneficial effect has been demonstrated for any agent tested. Despite this, individual cases may show a response to medication, essentially when a significant degree of inflammatory change is shown on biopsy. Under such circumstances, a trial of steroid (oral prednisolone 30–40 mg/day for 3–4 months) should be considered, and if successful, the dose slowly reduced, introducing steroid-sparing drugs if appropriate.

In all cases, non-pharmacological measures to support the patient are also crucial. Multi-disciplinary assessment from physiotherapists, occupational therapists and, if indicated, speech therapists, dietitians and colleagues from other medical disciplines, is recommended. Regular follow-up to assess progress and identify and treat potential complications is essential.

Table 9.40 Treatment of the idiopathic inflammatory myopathies, in the absence of evidence.

Steroids, aiming for rapid stabilization

Prednisolone 1 mg/kg/day by mouth until CK normal, then reduce (e.g. 5–10 mg monthly, with slower reduction for the last 20–30 mg)

If very acute resolution required: IV methylprednisolone 500 mg/5 days to initiate steroid course

Osteoporosis and gastric ulcer prophylaxis

Steroid-sparing agents (aiming to reduce side effects and maintain disease control)

First line

1. Azathioprine, starting at 1 mg/kg or below, and increasing by 25 mg every 1–2 months to a maximum of 2.5 mg/kg, as tolerated and guided by the degree of lymphocyte suppression and clinical response
   Thiopurine methyltransferase checked beforehand
   Blood monitoring of FBC and LFT necessary.
2. Methotrexate, increasing to 20–25 mg/day maximum *once weekly* with folic acid on other days, blood monitoring required; watch for pulmonary fibrosis and cirrhosis. NPSA guidelines available in UK

Second line

1. Ciclosporin: of use if first line drugs ineffective; blood monitoring required
2. IVIG: for refractory cases, particularly if deteriorating and rapid response sought
3. Cyclophosphamide, consider if poor response to other drugs (may be given as cycles of IV preparation in combination with other drugs; see peripheral nerve vasculitis)

CK, creatine kinase; FBC, full blood count; IV, intravenous; IVIG, intravenous immunoglobulin; LFT, liver function test; NPSA, National Patient Safety Agency,

Inflammatory myopathies associated with connective tissue disease

Although rheumatological diseases can lead to weakness through musculoskeletal deformity, neuropathy, muscle ischaemia or medication side effects, certain patterns of inflammatory myopathy are recognized, albeit infrequently. Systemic sclerosis occurs in conjunction with a DM-like picture in approximately 10% of cases, and 5–10% of people with SLE have a condition similar to PM. Sjögren's syndrome can rarely be seen with features similar to either DM or IBM. Myositis is very rare with either rheumatoid arthritis or polyarteritis nodosa. Muscle biopsy should be considered in any patient with a confirmed rheumatological illness, in particular if the CK is raised and EMG identifies myopathic features.

Inflammatory and other myopathies associated with infection

A number of viruses cause myositis. Common infections (Coxsackie, EBV, CMV, influenza) have all been associated with acute and chronic muscle inflammation, although such complications are rare and the underlying mechanism is unclear. A definite causative link has been established for the retroviruses HIV and human T-lymphocyte virus (HTLV-1) and myositis.

At seroconversion, HIV can lead to a polymyositis that can be explosive enough to provoke myoglobulinuria, and which is steroid-responsive. A nemaline rod myopathy may also develop at this stage of infection, with a raised CK and specific findings on biopsy. With the onset of AIDS, a necrotizing myopathy with proximal weakness, typically a normal CK and necrotic fibres on biopsy occurs. HIV wasting disease or 'slim' is frequently encountered in sub-Saharan Africa, but rarely in industrialized populations. 'Slim' is defined as more than 10% weight loss and weakness and fever or diarrhoea for at least 1 month, without any other causative condition. It appears to be caused by a combination of increased metabolic demand, anorexia and possible endocrine derangement and altered lipid metabolism. It leads to muscle wasting without myalgia, and when biopsied most typically shows type II fibre atrophy. Treatment is by improved nutrition and antiretrovirals. People with HIV are also at greater risk of infectious pyomyositis, which is typically multifocal and slower to evolve than the non-HIV-associated form. The range of causative organisms also differs with cryptococcus, toxoplasma, CMV and atypical mycobacteria implicated.

HTLV-1 is endemic in the Caribbean and Japan and most commonly leads to a slowly evolving myelopathy. It can alternatively provoke a polymyositis, which seems to follow expression of HTLV-1's tax-1 protein in muscle cells, rather than any sustained viral replication. HTLV-1 induced PM may respond to immunosuppression.

Non-viral infective myopathies occur with bacteria or parasites. Suppurative pyomyositis is typically a tropically acquired illness in which a staphylococcal abscess forms at the site of injury. In industrialized populations, immunosuppression from medication or conditions such as diabetes, liver disease or malignancy are more commonly associated than HIV. Staphylococci account for the great majority of infections but others including TB and fungi also occur. The diagnosis is largely clinical and treatment includes aspiration (which aids identification of the infective organism) and drainage if required and appropriate antibiotics.

Lyme disease, in addition to its more frequent CNS and nerve involvement, can unusually lead to myositis; this may be either a localized painful swelling or a rarer generalized dermatomyositis-like picture. Treatment is of the underlying spirochaete with appropriate antibiotics.

Some parasites cause focal or multi-focal muscle inflammation. Cestodes (cysticerci), nematodes (trichinella) and protozoa (toxoplasma, trypanosomes), all typically ingested in undercooked meat, can infect muscle. Muscle symptoms are often mild and self-limiting and it is involvement of the CNS that prompts identification and medication.

Other inflammatory myopathies

Granulomatous myopathies

Granulomatous myopathies present as a slowly evolving proximal weakness, possibly with dysphagia. Over time, flexion contractures may develop in the forearms and muscle hypertrophy may become evident. The serum CK is typically elevated and muscle biopsy demonstrates focal non-caseating granulomas. The differential is wide, including sarcoidosis, autoimmune conditions (rheumatoid arthritis, mixed connective tissue disease, Wegener's granulomatosis or in association with myasthenia gravis and thymoma) plus some infections (fungal, mycobacterial, protozoal). Many, but not all, respond to treatment with steroids.

Eosinophilic myopathic syndromes

Three forms of inflammatory myopathy are associated with eosinophilic infiltration of muscle, a systemic eosinophilia, or both. Eosinophilic polymyositis is similar to the classic PM described above, but occurs in conjunction with eosinophils, which are elevated in the circulation and prominently present on muscle biopsy. In eosinophilic fasciitis, pathological inflammation is limited to the fascia, and the fascia lata is the best site for confirmatory biopsy. Finally, dietary L-tryptophan, apparently contaminated by an acetaldehyde ditryptophan derivative, led to the eosinophilia myalgia syndrome. A marked eosinophilia developed with muscle pain and weakness with a scleroderma-like skin reaction and a peripheral neuropathy. Symptoms resolved after the medication was ended, although steroids were required to speed improvement in some cases.

Macrophagic myofasciitis

This is a rare but pathologically distinctive focal reaction at the site of vaccination, possibly directed against the aluminium hydroxide adjuvant of the vaccines. Originally described in France, after the adoption of hepatitis B vaccination, cases have now been reported from other countries. Many patients report systemic systems of fatigue, and CK can be significantly raised. Several years may elapse between the vaccination and the onset of the syndrome. Periodic acid–Schiff (PAS) positive macrophage infiltration of connective tissue is seen on biopsy. Steroid treatment is beneficial.

Myopathies associated with malignancy

Weakness may simply accompany tumour-induced cachexia, but cancers can cause a number of other muscle disorders.

Dermatomyositis and (less so) polymyositis can be associated with a range of malignancies (ovary, lung, gastrointestinal, non-Hodgkin's lymphoma) and, if so, have a worse prognosis.

An aggressive necrotizing myopathy is rarely seen in older patients with cancer (lung, gastrointestinal adenocarcinoma and breast). A rapidly progressive proximal weakness is typically accompanied by an elevated CK, while muscle biopsy demonstrates foci of necrosis. Steroids and treatment of the underlying tumour may help arrest symptoms.

Rare paraneoplastic antibody-driven myopathies have been reported. Waldenström's macroglobulinaemia can generate IgM against the muscle proteoglycan decorin. Myasthenia gravis, with or without underlying thymoma, can generate antibodies against skeletal muscle that cause rippling muscle disease: painful cramps with visible ripples of the muscle that often worsen with pyridostigmine but improve with immunosuppression.

Endocrine myopathies

Thyroid

Hypothyroidism frequently causes non-specific fatigue, myalgia and cramps and a raised CK. Untreated and over time a proximal symmetrical weakness can develop. The CK is not related to the level of weakness. Typically, the EMG shows myopathic changes and the histopathological findings are non-specific. Less commonly, myokymia may be seen and rarely severe muscle oedema may develop with subsequent rhabdomyolysis. The myopathy responds to thyroid replacement but is slow to do so.

Hyperthyroidism when severe is often associated with muscle weakness. Unlike hypothyroidism, distal muscles can be affected, sometimes in isolation. CK is not elevated. Symptoms are worse with severe and acute hyperthyroidism ('thyroid storm'). There is a rare inflammatory myopathy associated with hyperthyroidism, clinically similar to the idiopathic condition, and also causing a raised CK.

Adrenal

Cushing's syndrome leads to steroid myopathy as described below, while Addison's disease (whether primary or iatrogenic) typically causes myalgia, cramps and fatigue. Inadequate circulating levels of corticosteroids may lead to proximal weakness, which can lead to respiratory difficulty. Adequate steroid replacement is curative.

Parathyroid

Both inadequate and excessive levels of parathyroid hormone may lead to a mild progressive proximal myopathy. CK is more frequently raised in the former case, but normal in the latter.

Acromegaly

Untreated, excess growth hormone will cause a proximal weakness, sometimes with muscle hypertrophy and with an elevated CK. Some 50% of acromegalics show myopathic changes on EMG. Correction of the underlying condition leads to resolution of the myopathy.

Table 9.41 Drugs associated with myopathy.

Lipid-lowering: statins, fibrates, nicotinic acid, ezetimibe
Steroids
Abuse: alcohol, heroin, cocaine
Cardiac: amiodarone, perhexiline
Rheumatological treatments: colchicines, chloroquine, hydroxychloroquine
Other: ipecac (anorexics), streptokinase, zidovudine, α-interferon, d-penicillamine

Drugs and myopathy

A variety of drugs have been identified as causing a myopathy (Table 9.41). Some, such as steroids, will eventually cause a deleterious effect on all those who receive them. Others, such as statins, will do so to only some. The spectrum of drug-induced myopathy varies from an asymptomatic raised CK to profound weakness with rhabdomyolysis. Drugs may also worsen an existing muscle disease or, alternatively, unmask one that was previously hidden.

Statin myopathy

Statins inhibit the enzyme HMG CoA reductase, reducing the formation of cholesterol and also ubiquinone (coenzyme Q10). Series identify an eightfold risk of myopathy in those taking statins, raised to 42-fold if a fibrate is taken concurrently. This equates to about 1–6/10,000 treated. Approximately two million people in the UK were taking a statin in 2006, so only several hundred were expected to develop such side effects. It appears that the risk of statin-induced myopathy is dose-dependent but higher in the elderly or those with diabetes, hypothyroidism or concurrent renal or liver disease. Also at greater risk are those taking fibrates, especially gemfibrozil, or inhibitors of the hepatic enzyme CYP3A4 (including ciclosporin, proton pump inhibitors, various antifungals, calcium-channel blockers, SSRIs, grapefruit juice). The most common problem is of an asymptomatic elevation of CK, and the most frequent symptoms are of myalgia and cramps.

The classic pathological finding is a necrotizing myopathy which betrays the associated risk of rhabdomyolysis. Alternatively, statins can induce inflammatory or mitochondrial change (the latter with normal CK), or unmask an underlying metabolic condition.

A suggested management strategy for statin myopathy is given in Table 9.42. Stopping the statin usually leads to improvement within a few weeks, but myalgia and raised CK may persist and severe myopathy can leave permanent sequelae.

Zidovudine and other antiretrovirals

A toxic mitochondrial myopathy may follow the use of zidovudine (AZT), because of its inhibition of mitochondrial DNA replication. Those affected develop myalgia, exercise intolerance, proximal or generalized weakness and raised CK, usually after some time on the drug. A muscle biopsy is indicated, looking for cytochrome oxidase-negative fibres, not least to differentiate the diagnosis from that of HIV myositis. The myopathy usually resolves when zidovudine is stopped, although 3–4 months may be required. Zidovudine is also well recognized for its potential to expose a pre-existing carnitine deficiency.

Table 9.42 Management of statin myopathy (Mastaglia 2006).

Prevention	Start those at higher risk on lowest dose statin (e.g. pravastatin 10 mg/day)
CK raised without symptoms	Check CK again after 1 month; discontinue statin if CK rises further or symptoms develop
CK raised with symptoms	Stop statin. Consider co-enzyme Q10. Then: If symptoms resolve and the CK falls to normal, reinitiate statin at lowest dose If symptoms or elevated CK persist for 6 months off treatment, then perform muscle biopsy (to look for exposed inflammatory/mitochondrial myopathy) If the symptoms worsen or CK rises further, then proceed to urgent muscle biopsy

CK, creatine kinase.

Recently, the syndrome of nucleoside-associated lactic acidosis was been reported. Multiple symptoms including abdominal pain, vomiting, cough, shortness of breath, weight loss, together with myopathy and a painful axonal neuropathy develop subacutely in the first months of treatment. Cases have been reported up to 3 years after treatment began. Serum lactate is raised and muscle biopsy reveals necrosis plus mitochondrial abnormalities. Treatment is supportive, with fluids and bicarbonate to neutralize the acidosis, and the retroviral drug should be stopped. However, mortality is high at up to 50% and recovery is slow.

Steroid myopathy

Chronic administration of steroids reduces muscle protein synthesis, leading to insidious proximal weakness, especially of the quadriceps muscles. CK is not elevated and so any such rise necessitates separate investigation. Myopathy can occur at any dose but the incidence is highest with dexamethasone, betamethasone and triamcinolone, while for prednisolone daily doses in excess of 40 mg appear to confer the highest risk.

The pathological change is of selective type II (particularly IIB) fibre atrophy. The condition is usually reversible and so if

Table 9.43 Causes of rhabdomyolysis.

Acquired muscle disease	
Exertion	Extreme exertion, status epilepticus, status asthmaticus, prolonged involuntary movement
Crush	Multiple trauma, prolonged immobility (e.g. pre-operative, coma, torture)
Temperature	Pyrexia, exposure to extreme heat, burns
Ischaemia	Arterial occlusion, compartment syndrome, DIC, sickle cell disease
Metabolic	Hyper-/hyponatraemia, hypophosphotaemia, hyperosmolar state
Endocrine	Hypothyroidism, diabetic ketoacidosis, non-ketotic hyperosmolar coma
Alcohol	
Inflammatory	Polymyositis, dermatomyositis, vasculitis, paraneoplastic necrotizing myopathy
Drugs (see chapter 18)	Coma induced by alcohol, opioids or CNS depressants
	Agitation, e.g. following amphetamines. Possibly associated with serotonin syndrome or neuroleptic malignant syndrome
	Prolonged involuntary movements, e.g. drug-induced dystonic states
	Metabolic effects – statins, antidepressants, carbon monoxide, colchicines
Toxins	Snake bites
Infections	Viral – HSV, enterovirus, influenza A+B, CMV, EBV, adenovirus, HIV
	Bacterial – acute pyomyositis, staphylococcal/streptococcal
	Others – plasmodium, trichinella, toxoplasma
Inherited muscle disease	
Metabolic	Disorders of glycolytic – glycogenolytic pathway
	Disorders of fatty acid oxidation
	Disorders of purine cycle
	Mitochondrial respiratory chain
	Malignant hypothermia
Other hereditary muscle disease	e.g. congenital myopathy, dystrophinopathy, myotonic dystrophy

CMV, cytomegalovirus; DIC, disseminated intravascular coagulopathy; EBV, Epstein–Barr virus; HSV, herpes simplex virus.

possible steroids should be withdrawn. If withdrawal is not possible, the dosage should be reduced to the minimum and/or switched to an alternate-day regimen.

Rhabdomyolysis

Rhabdomyolysis is the breakdown of striated muscle fibres that leads to the release of muscle enzymes into the circulation. Myoglobinuria occurs when the haem-binding protein, myoglobulin, appears in the urine leading to a brownish discoloration with concentrations >250 μg/mL. The severity of rhabdomyolysis can vary from an asymptomatic elevation of muscle enzymes to severe electrolyte imbalance with acute renal failure. Rhabdomyolysis usually results from muscle injury because of trauma or other external causes (e.g. medication or intoxication) but may also develop if there is an underlying muscle disorder (Table 9.43). Therapeutic medication, substance abuse and toxins can cause rhabdomyolysis through a wide variety of mechanisms including prolonged coma, seizures, agitation, hypothermia, metabolic effects or direct myotoxicity.

Presentation depends on the cause of rhabdomyolysis but there is usually severe myalgia, muscle swelling and pigmenturia in association with greatly elevated CK (often >100,000). Compartment syndrome is characterized by severe muscle swelling in a limited anatomical space which may cause extreme pain and secondary vascular and neural compromise. The onset of renal failure may be manifest as oliguria and hypotension with haem pigmented casts. Electrolyte derangement arises from muscle lysis and renal failure and may include severe hyperkalaemia and hyperphosphotaemia with hypocalcaemia resulting from deposition of calcium salts within injured muscles. A secondary hypoalbuminaemia with hypotension, shock and cardiac arrhythmias may develop.

Management is treatment of the underlying disorder, correction of fluid and electrolyte abnormalities and prevention of renal failure. This usually involves plasma volume expansion with forced diuresis. The development of compartment syndrome may require fasciotomy.

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10 Multiple Sclerosis and Demyelinating Diseases

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Introduction

Multiple sclerosis is an inflammatory demyelinating disorder of the CNS. Although the characteristic pathological lesions were first described over 150 years ago, its aetiology and pathophysiology remain to be fully elucidated. However, advances in pathological, immunological and genetic techniques have provided a greater understanding of the disease mechanisms involved. The application of magnetic resonance imaging (MRI) over the last two decades has also provided important insights into the dynamics of the disease which have subsequently been used in diagnosis and monitoring. Multiple sclerosis is a complex disease with an unpredictable prognosis which may cause numerous and diverse symptoms and accumulating disability. Major advances in disease modification have been made in the last two decades and multiple sclerosis is no longer an 'untreatable' condition. However, current therapeutic agents have limited efficacy and do not prevent disease progression in the long term. Management requires a responsive and comprehensive approach involving multiple health disciplines. This chapter outlines the features of multiple sclerosis as we understand them today and reviews current practice in diagnosis and management. Other white matter diseases are also reviewed.

Epidemiology

It is estimated that there may be 85,000 people living with multiple sclerosis in the UK (population approximately 61 million). The prevalence is 100–150/100,000 population, with an annual incidence of new cases of 3.5–7/100,000. The incidence of multiple sclerosis worldwide tends to increase with increasing latitude, although there are clear exceptions. It is more common in temperate regions, such as northern Europe, North America and southern Australasia, but much rarer in the tropics. Geographical variations are seen over relatively small distances, e.g. it is more common in Scotland than in south-east England. Multiple sclerosis typically presents at 20–40 years of age. Females are more susceptible than males by a factor of approximately 2 : 1. There is evidence that the incidence of multiple sclerosis in females has been disproportionately increasing, and a steady increase in the sex ratio to over 3 : 1 has been reported in a Canadian population.

Migration studies

Some migration studies have demonstrated that people who migrate from one geographical area to another before adolescence are essentially subject to the same level of risk of the area to which they migrate; subjects who migrate after adolescence carry with them the incidence of the area from which they migrated. However, this age threshold is not evident in all studies, e.g. age at migration was not significantly associated with risk of multiple sclerosis in a migrant population in Australia. Although the risk of multiple sclerosis generally declines in migrants from high-risk to low-risk areas, the converse is not seen consistently in migrants from low-risk to high-risk areas. An increased risk is not seen in Caribbean and Asian immigrants to the UK initially, although the risk may increase over time, but the benefit is not passed on to the next generation. Migration may explain the higher incidence of multiple sclerosis than expected for latitude in countries such as Israel and South Africa.

Health economics

Multiple sclerosis is the most common cause of neurological disability in young adults and health care costs result in considerable financial burden to society. Many people are in education or employment at the time of diagnosis but, over time, reduced capacity to work and unemployment is common, which results in further indirect costs to society. In 2005, the cost of multiple sclerosis in the UK was estimated as over €40,000 per person with

Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

multiple sclerosis per year, with a total annual cost of over €3 billion. The total annual cost across Europe was estimated as €12.5 billion, with just over half arising from direct costs and the remainder from informal care and indirect costs. If intangible costs were included, the total annual cost was estimated as €23 billion.

Aetiology

The aetiology of multiple sclerosis is complex and cannot be ascribed to a single genetic or environmental factor. There is wide acceptance that interactions between genes and environmental factors lead to tissue injury by autoimmune mechanisms, implicated by immunological and pathological observations in people with multiple sclerosis and by extensive studies in the animal model of experimental allergic encephalomyelitis (EAE). Multiple sclerosis is weakly associated with other putative autoimmune disorders, including Hashimoto thyroiditis, psoriasis, inflammatory bowel disease and possibly rheumatoid arthritis, which may suggest that people with multiple sclerosis are predisposed to autoimmunity in general.

Genetic susceptibility

It is well recognized that genetic factors contribute to the occurrence of multiple sclerosis. Twin studies have demonstrated much higher concordance rates in monozygotic twins (approximately 30%) than dizygotic twins (approximately 5%) and family studies have shown that relatives of people with multiple sclerosis have a greater risk for the disease than the general population, approximately 3–5% in first degree relatives. No increased risk is seen in adopted relatives, and an intermediate risk is seen in half siblings, indicating that the familial risk is related to genetic rather than micro-environmental factors.

Genes that contribute to multiple sclerosis susceptibility have been difficult to identify because individually they exert only a relatively modest effect on disease risk. The only consistent genetic association and linkages identified are with alleles of the human lymphocyte antigen (HLA) class II region, part of the major histocompatibility complex (MHC); particularly HLA-DRB1*15 and HLA-DQB1*06. The role of class I alleles is inconsistent; recent reports suggest that some class I alleles may increase the risk of multiple sclerosis independently of the DRB1*15 and DQB1*06 alleles, while other class I alleles decrease the overall risk of multiple sclerosis in DRB1*15 and DQB1*06 carriers. There are likely to be multiple epistatic interactions at the HLA class I and II loci, with susceptibility and resistance alleles interacting to determine overall multiple sclerosis risk. HLA antigens are involved in immunoregulation, and so the genetic effect may be exerted through immunopathogenic mechanisms. More recently, multiple sclerosis has been associated with a polymorphism in the interleukin-7 receptor alpha gene (*IL7RA*). This is likely to be a real association as it has been replicated by several groups in multiple cohorts.

Environmental factors

Geographical gradients, migration studies and high discordant rates in monozygotic twins indicate that environment has a significant influence on the development of multiple sclerosis. Migration studies suggest that exposure to environmental factor(s) in early adolescence is associated with the development of multiple sclerosis. As multiple sclerosis may be uncommon in areas where sanitation is poor and the prevalence of parasitic infections is high, and as there is an increased incidence of autoimmune diseases in developed counties, the 'hygiene hypothesis' has been evoked. This suggests that exposure to infections in early childhood may protect against multiple sclerosis. However, the hygiene hypothesis has been largely discredited by conjugal pair, adopted children and sibship studies, which show no attributable risk to the familial micro-environment. Family-based genetic epidemiological approaches have found no evidence of non-genetic transmissibility within the familial micro-environment, which implies that the environment appears to influence the risk of multiple sclerosis at a population level. Several environmental factors have been proposed as aetiologically significant in multiple sclerosis, including transmissible agents and non-infectious factors.

Transmissible agents

Numerous transmissible agents have been implicated as the possible cause of multiple sclerosis. Suggested candidates include Epstein–Barr virus (EBV), human herpes virus type 6 (HHV-6), multiple sclerosis associated human endogenous retrovirus and *Chlamydia pneumoniae*. The epidemiological data associating EBV infection with multiple sclerosis is the strongest. A consistent finding is that almost all subjects with multiple sclerosis, >99%, are infected with EBV compared to only about 90% of control subjects. People who have had infectious mononucleosis or who have high titres of anti-EBV antibodies have a higher risk of developing multiple sclerosis compared to subjects who have not had infectious mononucleosis or who have low titres of anti-EBV antibodies. The association of EBV infection with multiple sclerosis may simply be a ubiquitous epiphenomenon that is required at the onset of the disease. There are several theories to explain how infection may cause multiple sclerosis but definitive evidence to suggest causation has been lacking. A recent pathological study has found evidence of EBV infection in B cells and plasma cells in the brain, with viral reactivation in acute lesions and ectopic B cell follicles, in multiple sclerosis but not in other neuro-inflammatory diseases. This still does not establish causation, but suggests that EBV persistence and reactivation may have an important role in pathogenesis. However, this finding has not yet been replicated in other studies.

Vitamin D and sunlight exposure

Two associated factors that have been recognized as a potential explanation for the link between geography, in particular latitude, and the incidence of multiple sclerosis are sunlight exposure and vitamin D status. Experimental and epidemiological data suggest that high levels of vitamin D decrease the risk of multiple sclerosis. Taking vitamin supplementation, which includes vitamin D, has been associated with a reduction in the risk of developing multiple sclerosis and small uncontrolled studies suggest vitamin D supplementation may decrease the incidence of relapses. A lower risk of multiple sclerosis is associated with high serum 25-hydroxy vitamin D levels in subjects of European extraction. In the northern hemisphere significantly fewer people with multiple sclerosis are born in November and significantly more are born in May, with a reversal of this ratio in the southern hemisphere. The fact that month of birth and risk of multiple sclerosis are associated implies an interaction with the environment that may act during gestation or shortly after birth. It has been proposed that this month of birth effect is linked to the vitamin D status of the mother but this has not been confirmed.

Smoking

Smoking prior to the onset of multiple sclerosis has emerged as a significant, albeit moderate, risk factor for the subsequent development of multiple sclerosis. It has been suggested that smoking may increase the risk of developing progressive disease, but a recent study found no effect of smoking on progression of disease. It has been hypothesized that smoking may explain the increase in incidence of multiple sclerosis in females, but this is unlikely as this increase predates the increase in incidence of female smokers.

Other environmental factors such as diet, alcohol consumption, recreational drug use, oral contraceptive pill exposure and vaccination have not been shown to increase the risk of multiple sclerosis.

Pathophysiology

The characteristic pathological feature of multiple sclerosis is the focal plaque or lesion. The lesions of multiple sclerosis were first depicted by Carswell in 1838 and the principal elements were described by Charcot in 1868 – demyelination, relative preservation of axons, gliosis and a variable amount of inflammation. This histological overview remains just as accurate today but the precise roles and inter-relationships of these elements in the pathogenesis of multiple sclerosis are still not fully elucidated. Furthermore, it is evident that the pathology of multiple sclerosis is not just confined to white matter lesions but involves the grey matter and macroscopically normal-appearing white matter (NAWM).

Pathology

Lesions occur throughout the CNS but particularly in the optic nerves, peri-ventricular white matter and corpus callosum, brainstem and cerebellar white matter, and cervical cord. Macroscopically, lesions are generally round or oval and, in broad terms, may be pink and soft, representing acute or active lesions, or grey and firm, representing chronic lesions (Plate 10.1). Brain atrophy and ventricular enlargement and atrophy of the spinal cord and optic nerves may be evident. Microscopically, acute lesions are characterized by active demyelination with marked inflammatory infiltrates, predominantly T lymphocytes and macrophages, associated with a variable degree of axonal damage and loss (Plate 10.1). In chronic lesions there is extensive loss of myelin, abundant astrocytic gliosis and axonal loss.

Table 10.1 Pathological classification of active multiple sclerosis lesions. (After Lucchinetti *et al.* 2000.)

I	T-cell/macrophage associated
II	Antibody/complement associated
III	Distal oligodendrogliopathy
IV	Oligodendrocyte degeneration in the peri-plaque white matter

Different patterns of demyelination in active lesions have been described. Lucchinetti and colleagues studied actively demyelinating lesions in a large sample of multiple sclerosis biopsy and postmortem samples and proposed four different patterns (Table 10.1). Inflammatory infiltrates, dominated by T lymphocytes and macrophages, were seen in all lesions. Patterns I and II were similar and lesions were typically sharply demarcated and centred on small veins and venules. High numbers of oligodendrocytes were seen. Pattern II was distinguished from Pattern I by prominent deposition of immunoglobulins and complement. Patterns III and IV were associated with signs of oligodendrocyte dystrophy. Pattern III lesions were diffuse with ill-defined borders. They were not centred on vessels and there was a preserved rim of myelin around vessels in some lesions. Unlike other patterns, where loss of myelin proteins was evenly distributed, there was a preferential loss of myelin-associated glycoprotein. There was pronounced loss of oligodendrocytes and oligodendrocyte apoptosis was seen. Pattern IV lesions were sharply demarcated. There was loss of oligodendrocytes and oligodendrocyte death was seen in a small rim of peri-lesional white matter. All active lesions within an individual patient exhibited the same pattern and there was no intra-individual heterogeneity. Patterns I and II were found in all clinical subtypes of multiple sclerosis. Pattern III was mainly found in people with disease duration of less than 2 months. Pattern IV lesions were only found in a variant of primary progressive disease. Therefore it was suggested that mechanisms of demyelination may be different in different subtypes and stages of the disease. However, this is not universally accepted. Different types of active lesions have been reported within individuals, and it has been suggested that the Pattern III lesions represent a very early stage in the development of acute lesions. Further study should be facilitated by the Multiple Sclerosis Lesion Project, an international collaboration, which has been designed to study the clinical, radiological and pathological correlates of multiple sclerosis lesions.

The role of inflammation in the pathogenesis of lesions also remains unclear. Axonal damage has been shown to occur not only in the presence of active inflammation, but also in chronic demyelinated lesions. Lesions in people who have died shortly after a relapse have been shown to have zones of extensive oligodendrocyte apoptosis and microglial activation in myelinated tissue (Pattern III) containing few or no lymphocytes or myelin phagocytes suggesting that lesion formation may be related to a process other than inflammation.

Active lesions are predominantly seen in acute relapsing disease and are rare in secondary and primary progressive disease, in which chronic lesions predominate. However, slow expansion of chronic lesions may occur in progressive disease. These lesions are characterized by a rim of activated microglia, at the edge of the lesion, which are associated with active demyelination.

Remyelination is seen in a large proportion of lesions, often at the edges of lesions, although it may be present throughout the lesion. Remyelination may be extensive and result in remyelination of the complete lesion, described pathologically as a shadow plaque. Although historically remyelination has been felt to occur predominantly in early relapsing disease, it is now apparent that extensive remyelination may also occur in progressive disease. It is not known why remyelination occurs in some lesions and not others.

Pathological abnormalities are also seen in NAWM. In contrast to the extensive inflammation seen in focal lesions, there may be a mild but diffuse inflammatory reaction in NAWM. Perivascular cuffing and diffuse inflammatory infiltrates and microglia activation are seen. Diffuse axonal injury is also evident. This does not correlate with the extent of lesions and so is not explained by Wallerian degeneration arising from focal lesions alone. Therefore, there appears to be a mechanism of axonal injury that is independent of focal lesions. Pathological changes are also not just confined to the white matter, and striking cortical demyelination may be seen. Subcortical lesions may extend into the cortex or small focal lesions may be present within the cortex, but extensive subpial demyelination may also occur. These diffuse changes in the NAWM and cortex are present far more extensively in progressive than in relapsing disease.

It has been previously suggested that relapses and disease progression may be occurring through distinct mechanisms, with relapses resulting from inflammatory demyelination and progression resulting from neurodegeneration. The recent advances in the elucidation of the immunopathology of multiple sclerosis provide support for a more unifying hypothesis. Multiple sclerosis typically starts with acute inflammation, arising from specific immune mechanisms, which are discussed below, resulting in focal inflammatory demyelinating lesions. Over time, inflammation becomes sequestered within the CNS. This inflammation may be non-specific and low grade but it drives the slow expansion of chronic lesions and the diffuse injury in the NAWM and cortex.

Autoimmune pathogenesis

The first step in the autoimmune pathogenesis of multiple sclerosis is believed to be that an environmental agent(s) combined with a genetic predisposition resulting in the production of pathological autoreactive T cells. After a latent period of 10–20 years a breakdown in immunological tolerance, possibly by a systemic trigger such as a non-specific viral infection or exposure to a superantigen, activates these autoreactive T cells.

During the normal process of immunosurveillance, memory $CD4^+$ T-helper (Th) cells selectively cross the blood–brain barrier, through a process involving the interaction of their cell surface adhesion molecules with those expressed on CNS endothelium. Once within the peri-vascular space, these cells are presumably activated by professional antigen-presenting cells (probably macrophages or microglia) to proliferate and produce pro-inflammatory cytokines. Antigen recognition occurs via the tri-molecular complex, consisting of HLA, T-cell receptor and CD3 molecules. This requires additional co-stimulatory signals, e.g. interactions between HLA-MHC I and II molecules and their respective CD8 and CD4 molecules, and CD28/B7-2/1 pairs.

Humoral immunity appears to have an important role in multiple sclerosis, and intrathecal antibody synthesis is characteristic of the disease. The presence of B-cell clonal expansion in CSF and in lesions indicates an antigen-driven response within the CNS. Ectopic B-cell follicles have also been found in the meninges and are anatomically associated with subpial cortical lesions, providing further evidence that B cells are involved in immunopathogenesis.

Potential autoantigens implicated in the pathogenesis of multiple sclerosis include myelin basic protein, proteolipid protein, myelin-associated glycoprotein, myelin oligodendrocyte glycoprotein and alpha-B crystallin. The presence of specific cytokines, e.g. interleukin 12 (IL12) and IL23, govern the type of Th response. Th1-like cytokines (IL2, interferon γ and tumour necrosis factor α [TNF-α]) or Th23-like cytokines (IL17) initiate a cell-mediated inflammatory cascade which activates macrophages, microglia, astrocytes and endothelial cells. This results in further cytokine production and recruitment of inflammatory cells by the up-regulation of adhesion molecule expression on endothelial cells and by the production of chemo-attractants, such as chemokines. Astrocytes and macrophages produce mutually stimulating cytokines (IL1 and TNF-α). These and other pro-inflammatory T-cell cytokines up-regulate the production of numerous mediators of inflammation, which are toxic to oligodendrocytes, axons and neurones. These substances include TNF-α, free oxygen and nitrogen radicals, complement, proteases and eicosanoids.

Autoantibodies, particularly to surface myelin antigens, may be crucial to the development of demyelination. Autoantibodies to axonal elements, e.g. gangliosides and neurofilaments, may have functional consequences and may contribute to conduction abnormalities and axonal loss. In addition to myelin damage, programmed cell death or apoptosis of the oligodendrocyte may occur as a result of oxidative stress and death signalling induced by TNF-α. Antibodies and complement assist Fc-receptor mediated phagocytosis by opsonization. Phagocytosis also occurs via the macrophage scavenger and low-density lipoprotein receptors.

T-regulatory cells and immunomodulatory cytokines produced by these cells are important in down-regulating and controlling the focal inflammation. Elimination of autoreactive T cells by apoptosis may be important in controlling inflammation.

The combination of both cell and humorally-mediated inflammatory cascades causes oligodendrocyte, axonal and neuronal toxicity, which in turn is believed to release sequestered CNS antigens which are hypothesized to initiate further cycles of autoimmune-induced inflammation via intra- or intermolecular antigen determinant spreading.

Demyelination results in a reduction in the safety factor of conduction, with complete or intermittent conduction block, which produces clinical symptoms and signs, some of which may be intermittent. Resolution of inflammation and oedema initially may result in clinical improvement. Over a longer time, remyelination and/or axonal plasticity (synthesis of new sodium channels along demyelinated axonal segments) restores axonal conduction, albeit with a reduced safety factor of conduction, which results in remission. There is evidence that growth factors produced as part of the inflammatory response stimulate the process of remyelination. Transient neurological symptoms may occur secondary to the residual reversible conduction block, typically in relation to fatigue, changes in body temperature and systemic inflammation. Ephaptic transmission may cause paroxysmal positive neurological symptoms. Axonal loss and gliosis, as a consequence of acute or diffuse injury, cause permanent neurological impairment and disability.

Clinical course

Multiple sclerosis is characterized by lesions disseminated throughout the CNS, which may appear, disappear or gradually worsen over time, and this is reflected in its clinical presentation and course. Its presentation is variable and its course and prognosis are unpredictable, although broad clinical categories of the disease are well recognized.

Types of multiple sclerosis

Clinical disease activity in multiple sclerosis may manifest as relapses or insidious progression. According to the occurrence and timing of these features, four main categories of multiple sclerosis have been outlined in the widely accepted classification of Lublin and Reingold (Figure 10.1).

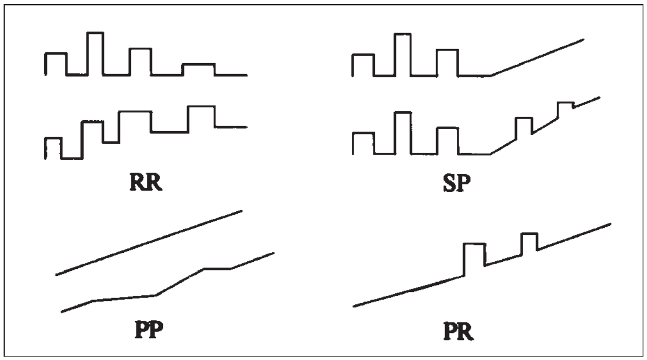


Figure 10.1 Clinical course of multiple sclerosis: illustration of the relationship between increasing disability and time in the different types of multiple sclerosis (PP, primary progressive; PR, progressive relapsing; RR, relapsing remitting; SP, secondary progressive). (After Lublin & Reingold 1996.)

Relapsing remitting multiple sclerosis

Approximately 85% of individuals present with relapses and remissions. A relapse is defined as an episode of acute or subacute neurological dysfunction lasting a minimum of 24 hours. A relapse usually evolves over days or weeks, plateaus and then remits to a variable degree, from minimal resolution to complete recovery. Further relapses may then occur at irregular intervals. The average relapse frequency in the relapsing remitting phase of the disease is approximately one relapse per year.

Secondary progressive multiple sclerosis

Relapsing remitting multiple sclerosis may evolve into a gradually progressive course with accumulating irreversible neurological deficit and disability, classified as secondary progressive multiple sclerosis. The proportion of people developing secondary progressive disease increases with length of follow-up. In a large Canadian natural history study, 41% of people with relapsing remitting multiple sclerosis entered the secondary progressive phase within 6–10 years of disease onset increasing to 58% between 11 and 15 years after onset. After 20 years approximately 80% had developed secondary progressive multiple sclerosis. Superimposed relapses may continue to occur in the secondary progressive phase, although less frequently as the disease progresses.

Primary progressive multiple sclerosis

In primary progressive multiple sclerosis there is insidious disease progression from onset, resulting in gradual accumulation of neurological deficit or disability, without relapse or remission. It accounts for approximately 10–15% of multiple sclerosis. Males and females are affected with equal frequency. The average age of onset is older in primary progressive multiple sclerosis, approximately 40 years compared to 30 years in relapsing remitting multiple sclerosis.

Progressive relapsing multiple sclerosis

Progressive relapsing multiple sclerosis refers to the small number of people who have progressive disease from onset with superimposed relapses, but the term is now rarely used. Insidious progression is the predominant feature and relapses are usually mild. Progressive relapsing multiple sclerosis is considered to be largely similar to primary progressive multiple sclerosis. Approximately one-quarter of people initially diagnosed with primary progressive multiple sclerosis will later have relapses, and a relapse may occur decades after disease onset.

Natural history and prognosis

The natural history of multiple sclerosis is extremely variable. The spectrum of disease activity ranges from clinically asymptomatic demyelinating lesions, detected incidentally on imaging or at postmortem, to an aggressive course with rapidly accumulating disability. It is not possible to predict prognosis in an individual, but natural history studies have provided data on disease progression in different multiple sclerosis populations.

Clinically isolated syndromes

A clinically isolated syndrome refers to a first acute episode suggestive of CNS demyelination, and it may be the first presentation of multiple sclerosis. The average risk of developing multiple sclerosis following a clinically isolated syndrome has been reported as between 30% and 70%, although the risk increases with the length of follow-up. People presenting with unilateral optic neuritis may have a lower risk of converting to multiple sclerosis than other clinical presentations. Abnormal MRI at first presentation has been consistently shown to confer a higher risk of conversion to multiple sclerosis than if MRI is normal. Long-term follow-up studies, ranging from 7 to 20 years, have reported the development of multiple sclerosis to occur in 56–88% of people with lesions on MRI and in 8–22% of those with a normal scan. The lesion number and load at first presentation may also have prognostic relevance, with higher lesions loads modestly predictive of the likelihood of developing disability in the long term.

Established multiple sclerosis

Natural history studies have conventionally assessed disease progression in multiple sclerosis by measuring the time taken to reach disability milestones. Such studies have shown that the median time to reach a level of disability requiring assistance for walking is between 15 and 30 years.

There has been debate as to the effect of the disease type on long-term prognosis. Relapsing remitting multiple sclerosis has been felt to carry a better prognosis, but a French natural history study from a single large centre reported that disease progression in the long term is largely independent of disease type. However, this requires replication in other studies. Although accumulation of irreversible disability is slower in the relapsing and remitting phase, once the secondary progressive phase is entered the initial course does not seem to significantly influence long-term prognosis.

The influence of residual disability from relapses on long-term accumulation of disability has been similarly debated. Residual neurological deficit following a relapse is common. For example, an increase in disability was demonstrated in one study in up to 42% of people at 2 months following a relapse. However, further recovery may take place over a longer time. Analysis of the placebo arms of treatment trials in relapsing remitting multiple sclerosis has suggested that relapses, although resulting in confirmed disability over 6 months, do not seem to have a consistent effect on the development of sustained disability over the course of a typical study (mean 2.66 years). Further study is required to understand the effect of relapses on long-term disability.

The age of onset does not seem to significantly influence long-term prognosis. Younger age of onset has previously been considered a good prognostic marker but this is not really the case as, although the time to develop permanent disability may take longer, disability still occurs at a younger age. The older age of onset associated with primary progressive multiple sclerosis has also previously been felt to be a poorer prognostic marker. However, the average age of onset in primary progressive multiple sclerosis is similar to that of the progressive phase in secondary progressive multiple sclerosis. The rate of progression is also similar in the primary and secondary progressive groups, with disability milestones being reached at similar ages.

Male sex has been suggested to be associated with a poorer prognosis, but recent studies suggest that this may not be clear-cut. Factors reported to be associated with a more favourable prognosis include monosymptomatic onset, afferent symptoms (sensory, optic neuritis) at onset, complete recovery from first attack, a long interval between first and second relapses and a low relapse frequency in early disease. However, such associations are weak and it is not possible to reliably predict individual prognosis.

Benign multiple sclerosis

Benign multiple sclerosis refers to a disease course with accumulation of minimal or no disability. There is no consensus definition, but it is often taken as an Expanded Disability Status Scale (EDSS) score ≤3 (Table 10.2) at 10–15 years after disease onset. A systematic review of published studies has reported the frequency of benign multiple sclerosis as 26.7%, but the proportion of people with benign disease decreases with length of follow-up. In a large British Columbian cohort only half of those with benign disease at 10 years still fulfilled the criteria at 20 years, with the remainder having developed secondary progression. There are no reliable indicators of a benign course, although follow-up over 20 years in a US cohort found that the longer the disease duration and the lesser the disability, the more likely an individual was to remain stable. It is well recognized that even long-standing benign disease may progress with the development of severe disability.

Aggressive multiple sclerosis

An aggressive or malignant disease course may result from severe or frequent relapses with little or no neurological recovery or from rapid disease progression. However, aggressive disease is uncommon and early death in multiple sclerosis is rare.

The Marburg variant of multiple sclerosis refers to an acute fulminant disease course, usually monophasic, which may result in death within a few months. Its clinical presentation relates to its site, which may be cerebral, brainstem or spinal cord. In cerebral presentations, confusion and seizures may occur. MRI shows large lesions, correlating to destructive hypercellular demyelinating lesions on neuropathological examination, which typically enhance and may have associated oedema and mass

Table 10.2 Expanded Disability Status Scale (EDSS). Functional systems (FS) are pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual and cerebral. (Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). *Neurology* 1983: 33: 1444–1452.)

0.0	Normal neurological examination
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Minimal disability in two FS
3.0	Moderate disability in one FS or mild disability in three or four FS, although fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS and mild disability in one or two FS; or moderate disability in two FS; or mild disability in five FS
4.0	Fully ambulatory without aid, self-sufficient up and about some 12 hours a day despite relatively severe disability in one FS or combinations exceeding limits of previous steps; able to walk without aid or rest some 500 m
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; able to walk without aid or rest some 300 m
5.0	Ambulatory without aid or rest for about 200 m; disability severe enough to impair full daily activities (e.g. to work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 m, disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 m with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 m with or without resting
7.0	Unable to walk beyond approximately 5 m even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone, up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer, wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions
9.0	Helpless bed patient; can communicate and eat
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

MS, multiple sclerosis.

effect (Figure 10.2). The condition must also be distinguished from acute disseminated encephalomyelitis, acute haemorrhagic leucoencephalitis and vasculitis.

Baló concentric sclerosis refers to a particular neuropathological lesion variant, which may also be evident on MRI, characterized by alternating concentric layers of myelin loss and relative preservation of myelin. It may be seen in association with a fulminant course, although it may also occur in more benign disease.

Mortality

Mortality rates are increased compared to the general population. The average life expectancy in multiple sclerosis in a Canadian study was reported as 6–7 years less than a control population. The cause of death in approximately half was directly attributed to complications of multiple sclerosis. A significantly increased incidence of suicide was seen in the multiple sclerosis population of 7.5 times that of the general poulation. A more recent Danish study reported survival in multiple sclerosis to be approximately 10 years shorter than the general population. The suicide rate was more than twice the rate of the general population.

Early onset multiple sclerosis

Although rare, the onset of multiple sclerosis may be in childhood. Early onset, before the age of 16 years, occurs in approximately 2–5% of individuals. A relapsing remitting disease onset is typical, and a primary progressive course is much rarer than in adult onset disease. Prognosis may be considered better in that the time to develop disability is longer than in adult onset multiple sclerosis, but overall individuals develop disability at a younger age. Over half are likely to develop secondary progressive multiple sclerosis by the age of 30 years. The paediatric multiple sclerosis population may be an ideal group in which to study aetiological factors, and there has been a recent upsurge of interest in this group. A large international collaboration has recently reported that paediatric multiple sclerosis may be associated with exposure to EBV, but not with other common childhood viral infections.

Factors affecting relapse activity

Various health and lifestyle factors have been proposed to affect relapse activity in multiple sclerosis. It is important that people with multiple sclerosis are aware of these factors to facilitate informed decisions regarding their lifestyle.

Infections

Systemic infections may trigger a relapse or exacerbate existing symptoms of multiple sclerosis. An association between common viral and bacterial infections and risk of relapse has been documented, but such infections are difficult to avoid. Infections may

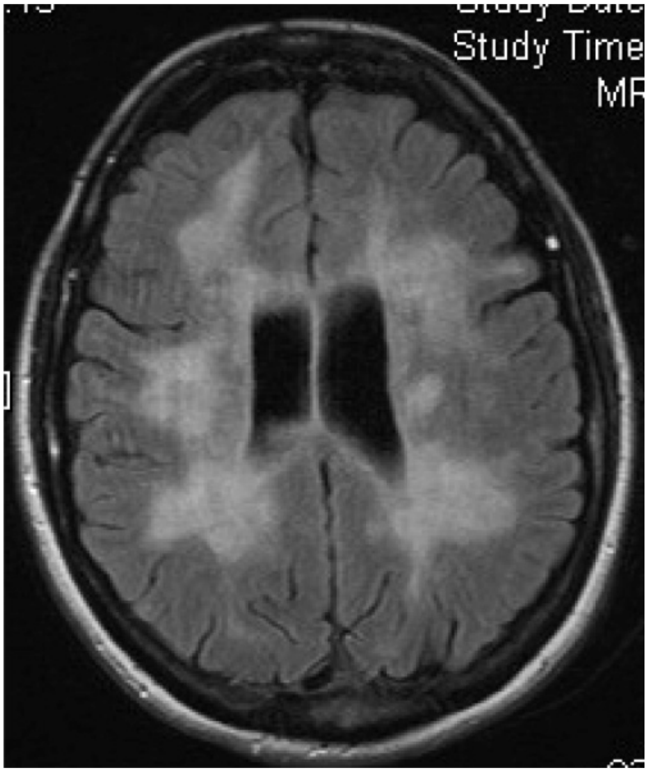


Figure 10.2 Marburg variant of multiple sclerosis (MRI T1W axial).

occur as a complication of multiple sclerosis, e.g. urinary tract infections resulting from retention and chest infections resulting from aspiration. Therefore, addressing the underlying cause of infections may be preventative and, where possible, infections should be anticipated and treated early. Cigarette smoking, aside from its well-known health risks, may increase the occurrence of respiratory tract infections and should be discouraged.

Pregnancy

The effect of pregnancy on disease activity is an important concern among women of childbearing age. A large prospective study of pregnancy in multiple sclerosis confirmed that relapse rate declines during pregnancy, especially in the third trimester, increases during the first 3 months postpartum and then returns to pre-pregnancy rate. The incidence of postpartum relapse was 28%. An increased relapse rate in the pre-pregnancy year and during pregnancy, and higher disability at pregnancy onset, were associated with a higher risk of postpartum relapse. Epidural analgesia and breastfeeding were not found to increase the risk of relapse.

Stress

Prospective studies have reported stressful life events to be associated with an increased risk of relapse. A meta-analysis also supported an association between stressful life events and subsequent relapses although did not link relapse to specific stressors. Physical trauma has been proposed to trigger relapses but a systematic review of the evidence has not supported this link.

Diet

Despite popular interest in the effect of diet on multiple sclerosis there is little evidence to support an association between dietary factors and disease activity. A systematic review concluded that no dietary intervention has been shown to significantly affect disease progression. Linoleic acid, an omega-6 fatty acid, was associated with slight decreases in relapse rate and severity, but the studies were small and of limited design.

Vaccines

The question of whether vaccination may immunologically trigger a relapse has been investigated and there is no clear evidence to support this hypothesis. Most vaccines have not been investigated prospectively, but a double blind, placebo controlled study of influenza vaccine showed no effect on relapse rate or disease progression. There has been particular concern regarding hepatitis B vaccination but a large case cross-over study found no increased risk of relapse following hepatitis B or any vaccination. Current expert opinion is that vaccinations are not contraindicated in multiple sclerosis, and national guidelines recommend that people with multiple sclerosis should be offered vaccination against influenza. However, it must not be forgotten that live vaccines may be contraindicated in individuals on immunosuppressant therapy.

Clinical features

Multiple sclerosis can cause a wide variety of symptoms mirroring involvement of any part of the CNS. The spinal cord, optic nerves and brainstem are commonly involved sites. In a European database of clinically isolated syndromes, 46% of individuals presented with a spinal cord syndrome, 21% with optic neuritis and 10% with a brainstem syndrome. The presentation was polysymptomatic in 23% of cases. Differences in presenting symptoms are seen between disease types. In relapsing remitting multiple sclerosis, the most common symptoms are sensory and visual, whereas in primary progressive disease the most usual presentation is locomotor. During the course of the disease a multitude of symptoms may occur. These include weakness, spasticity, numbness, paraesthesia, pain, visual loss, diplopia, ataxia, tremor, vertigo, sphincter and sexual dysfunction, dysphagia, dysarthria, repiratory dysfunction, temperature sensitivity, fatigue, cognitive and psychiatric disturbance.

There are no symptoms or signs that are pathognomonic for multiple sclerosis, although characteristic clinical features are seen. Optic neuritis is a common manifestation. It presents with eye pain, which is exacerbated by eye movement, and blurring of vision. The visual impairment may progress over a few days, but not usually longer than 1–2 weeks. Continued progressive visual failure or loss of perception to light should alert to the possibility of alternative diagnoses. On examination, colour vision and visual acuity are impaired and a scotoma, classically central, may be detected. The optic disc may be normal but swelling may be present, and pallor of the optic disc may develop later. A relative afferent pupillary defect is usually present.

Diplopia may be a presenting symptom and usually is symptomatic of a VIth nerve palsy or an internuclear ophthalmoplegia. As the disease advances, unilateral or bilateral internuclear ophthalmoplegia, identified on conjugate lateral gaze as impaired adduction on the side of the lesion and nystagmus of the abducting eye, is commonly seen but may often be asymptomatic.

A partial spinal cord syndrome is a frequent presentation. Typically, altered sensation starts in one foot and spreads to involve both legs and, to a varying extent, ascends to the trunk and arms. Variable degrees of numbness and tingling may occur but complete loss of sensation is unusual. On examination, all sensory modalities may be impaired and a sensory level may be discerned although, as the relapse recovers, a persistent bilateral sensory level is uncommon. Oppenheim hand, a functionally useless hand caused by loss of position sense, may be a characteristic presentation of a lesion in the posterior columns of the cervical cord.

Motor involvement becomes more common as the disease advances and weakness is a prominent symptom. Weakness is usually greater in the legs than the arms, and paraparesis is frequently asymmetrical. Spasticity may manifest as stiffness, clonus or spasms. On examination, signs usually reflect upper motor neurone involvement with hypertonia, hyper-reflexia and positive Babinski responses. However, focal wasting, flaccidity and loss of tendon reflexes may be seen, and may result from denervation in the spinal cord.

Spinal cord involvement also commonly results in bladder and bowel disturbance. Bladder disturbance may result from a combination of detrusor hyper-reflexia, manifesting as urgency, frequency and incontinence, and incomplete emptying because of sphincter dyssynergia and poorly sustained detrusor contractions, resulting in hesitancy and incomplete emptying. Constipation is the most common bowel symptom, although urgency and incontinence is not infrequent. Sexual function in males and females is frequently affected, because of central neurological dysfunction, although psychological and other factors may also contribute.

An initial cerebellar presentation is uncommon but cerebellar involvement is frequent during the course of the disease, evidenced by nystagmus, dysarthria, limb ataxia and intention tremor and truncal ataxia. Gait ataxia may contribute to the classic spastic ataxic gait, but it may also cause disabling gait disturbance in the absence of significant weakness and spasticity.

Fatigue may be one of the most disabling symptoms in multiple sclerosis, and may impact on all activities. An exercise-induced motor fatigue and an unprovoked but severe generalized exhaustion may be reported. Fatigue appears to be related to electrophysiological and immunological effects of multiple sclerosis, and is often worse during relapses, but disturbed sleep, medication and depression may also be contributory factors. Heat sensitivity is a common symptom, caused by the increased temperature inducing slowing of nerve conduction. Uhthoff phenomenon refers to the transient blurring of vision on exercise or in hot environments brought about by underlying optic nerve disease.

Cognitive impairment is well documented to occur in multiple sclerosis and mild deficits may be apparent in early disease. Attention, information processing, memory and executive functions are predominantly affected. Severe dementia may occur but, particularly in early disease, may suggest an alternate diagnosis. Depression occurs more frequently than in the general population but is usually mild and is often reactive to the diagnosis and ensuing neurological deficits. Emotional lability, with pathological crying or laughing, may occur. Psychosis is an uncommon manifestation of multiple sclerosis, but may rarely be the presenting episode.

Pain is common in multiple sclerosis and is usually chronic. It is often myelopathic in origin, typically resulting in a burning pain in the legs and hands. Paroxysmal pain may occur, most notably trigeminal neuralgia. Pain may also result indirectly from other related problems such as spasms and musculoskeletal complications.

A characteristic feature of multiple sclerosis is the occurrence of paroxysmal symptoms, resulting from electrical instability within lesions. A typical episode is of acute onset with symptoms of short duration, less than 2 minutes, occurring up to 30 or more times a day. The whole episode usually resolves spontaneously within a few weeks to months. The nature of the symptoms reflects the underlying site of the lesion. Infratentorial lesions may result in trigeminal neuralgia and paroxysmal dysarthria and ataxia. Tonic spasms, painful tonic contractions usually involving one or two limbs unilaterally, may arise from sites in the corticospinal tract. Other paroxysmal sensory disturbances may occur and paroxysmal itching is described.

Other positive symptoms include Lhermitte's symptom, a brief electrical sensation radiating down the back into the legs or arms precipitated by neck flexion, caused by a lesion in the cervical cord, and phosphenes resulting from optic nerve demyelination. Lesions involving the facial nucleus or nerve may cause hemifacial spasm or facial myokymia. Epilepsy, originating from juxtacortical or cortical lesions, is seen 2–3 times more commonly than in the general population, and rarely may be the presenting symptom.

Diagnosis

Multiple sclerosis is a clinical diagnosis that requires appropriate expertise to confirm evidence of CNS lesions disseminated in time and space and to exclude other diseases. Investigations may be used to:

1. Exclude other diseases;
2. Provide evidence of dissemination in time and space; and
3. Provide evidence of immunological disturbance.

Diagnostic investigations

Magnetic resonance imaging

The plaques of white matter demyelination in multiple sclerosis are readily visualized on MRI by virtue of an increase in the amount and mobility of water protons in the lesions. The standard imaging sequence is a T2-weighted spin echo or fast spin echo, with an additional fast FLAIR (fluid attenuated inversion recovery) sequence that suppresses signal from cerebrospinal fluid (CSF) and increases the conspicuity of cerebral hemisphere lesions.

The value of MRI in diagnosis comes through its high sensitivity for detecting clinically silent lesions, and showing them in characteristic locations; the detection of blood–brain barrier breakdown in acute lesions using gadolinium-enhanced T1-weighted MRI is also a useful finding. MRI may be normal in clinically definite multiple sclerosis, but this is unusual: lesions are seen in the brain in approximately 95% and spinal cord lesions in approximately 70% with a clinically definite diagnosis. The characteristic locations for foci of demyelination are: periventricular, corpus callosum, juxtacortical, brainstem, cerebellar white matter and spinal cord (Figure 10.3). Lesions are usually small (3–10 mm diameter), may have an oval or rounded shape, and usually extend to the parenchymal surface in the brainstem and spinal cord. Cord lesions are most often seen in a posterior or lateral location, involve white and grey matter, and affect only part of the cord in cross-section (Figure 10.4). Gadolinium enhancement is invariable in new lesions in relapsing multiple sclerosis, can be homogeneous or ring-shaped, and lasts an average of 2–6 weeks (Figure 10.5).

In people with a clinically isolated syndrome (CIS), clinically silent cerebral white matter lesions are seen in 50–70%. The presence of MRI lesions confers a relatively high risk for future development of clinically definite multiple sclerosis as already discussed. Development of new T2 or gadolinium-enhancing lesions on follow-up MRI increases the likelihood of early clinical relapses and, accordingly, the development of clinically definite multiple sclerosis.

The major limitation of MRI is specificity: there are many other causes of cerebral white matter lesions (Table 10.3). Small vessel disease is an especially common cause of areas of T2 hyperintensity on white matter and over one-third of the general population aged over 50 years will exhibit areas of high signal. These are small, and mainly subcortical rather than peri-ventricular. Basal ganglia involvement is not uncommon and central pontine abnormalities are also seen (unlike multiple sclerosis, not extending to the surface). Cord lesions do not occur with ageing per se and their detection in older patients is a particularly useful pointer to demyelination.

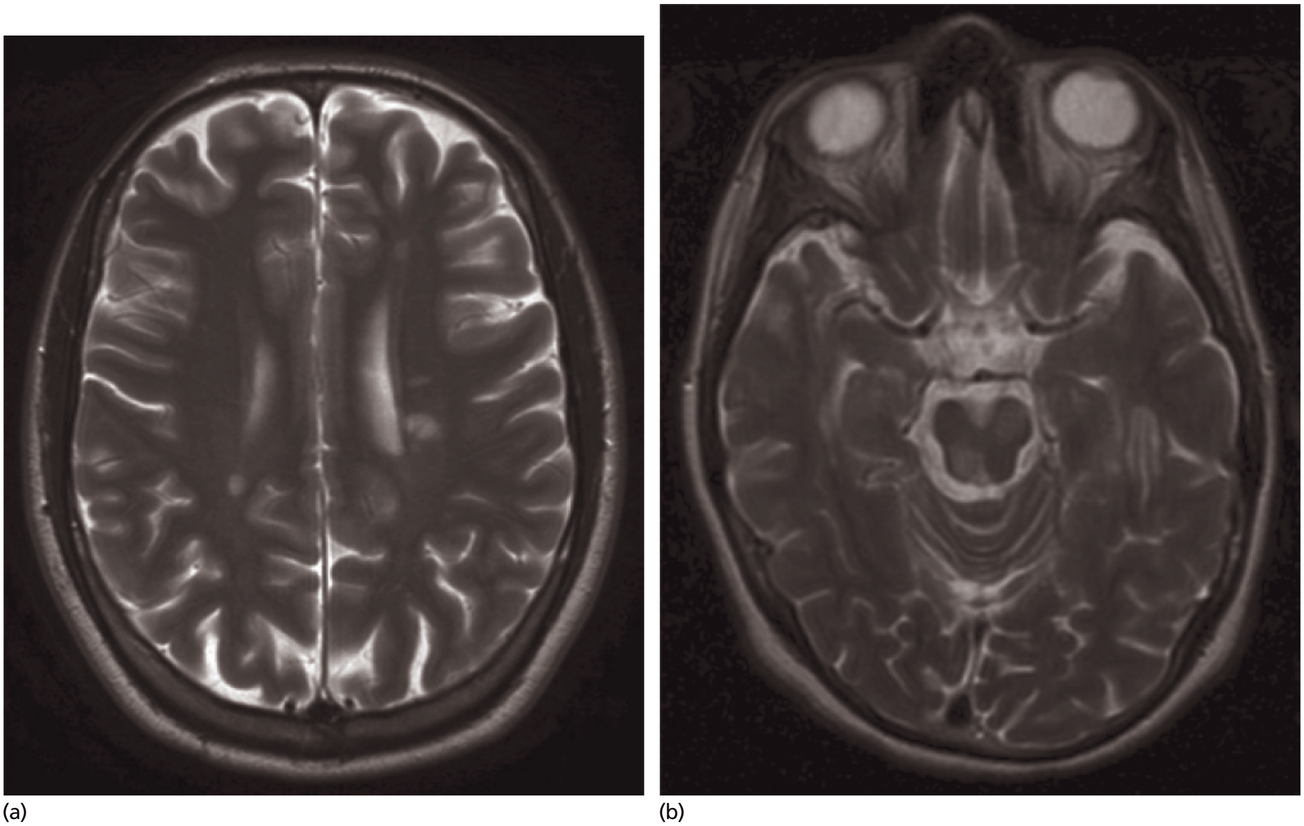

(a) (b)

Figure 10.3 Typical lesions in multiple sclerosis: (a) periventricular; (b) infra-tentorial (MRI T2W axial).

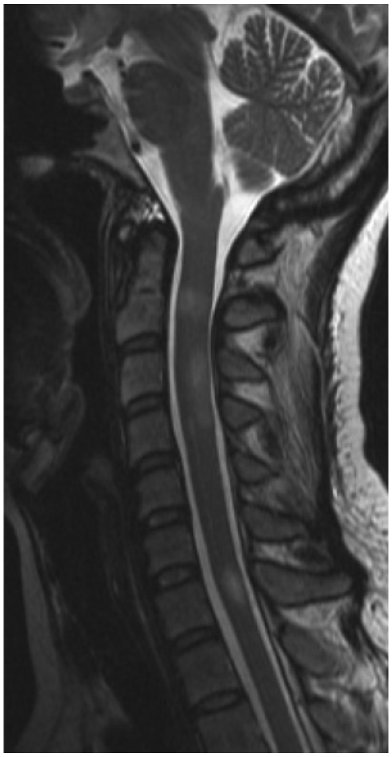
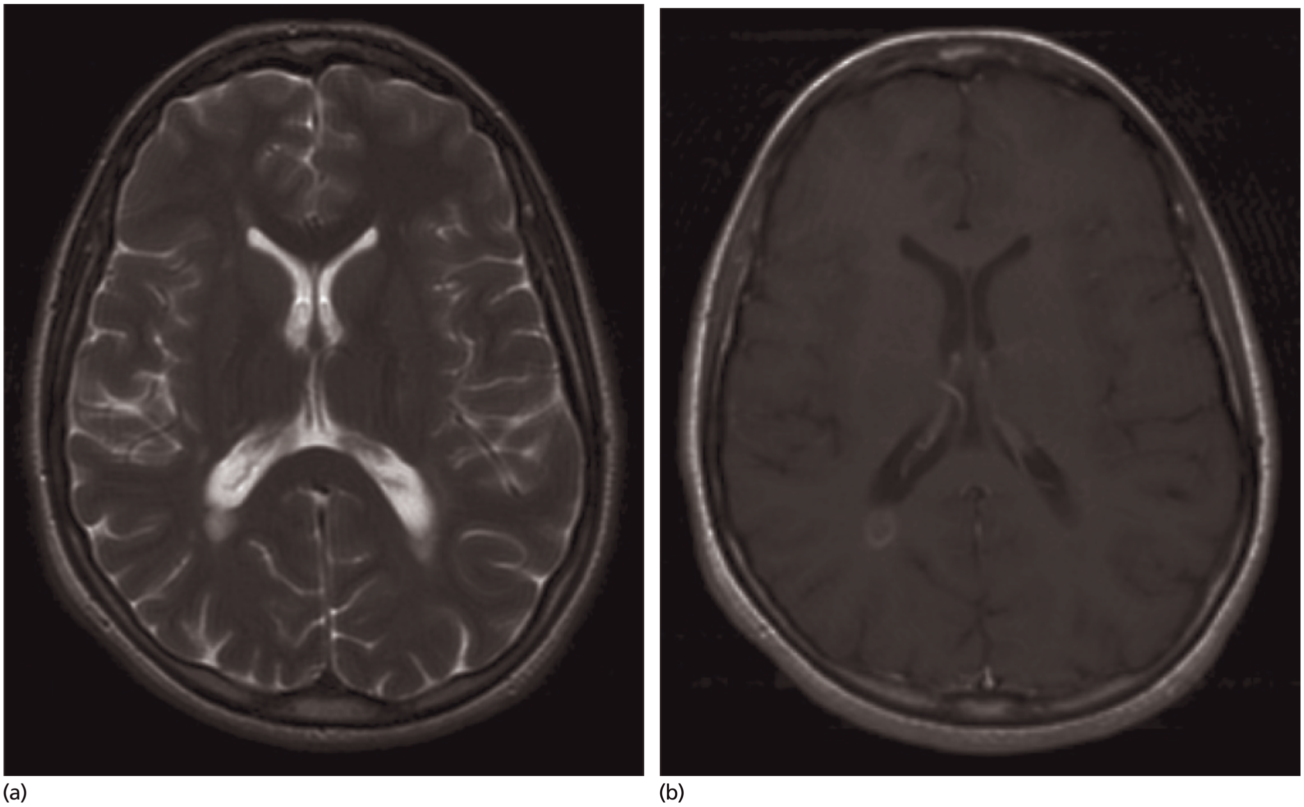


Figure 10.4 Typical lesions in the cervical cord in multiple sclerosis (MRI T2W sagittal).



(a) (b)

Figure 10.5 Typical Lesions in multiple sclerosis: (a) an acute periventricular lesion (MRI T2W); (b) associated gadolinium enhancement (MRI T1W axial).

Table 10.3 Differential diagnosis of white matter lesions on magnetic resonance imaging (MRI).

Inflammatory
Multiple sclerosis
Acute disseminated encephalomyelitis
Neuromyelitis optica
Vasculitis (including SLE, Sjögren's syndrome)
Sarcoidosis
Behçet's disease
Primary angiitis of the CNS

Vascular
Small vessel disease
Antiphospholipid syndrome
CADASIL

Infectious
Progressive multifocal leucoencephalopathy
HIV encephalitis
Viral encephalitis
Lyme's disease
Whipple's disease
Syphilis
Subacute sclerosing panencephalitis
Intracerebral abscesses
Tuberculosis/fungal infections

Metabolic
Pontine/extra-pontine myelinolysis
Phenylketonuria
Vitamin B_{12} deficiency
Hyperhomocysteinaemia
Cerebrotendinous xanthomatosis

Leucodystrophies
Adrenoleucodystrophy/adrenomyeloneuropathy
Globoid cell leucodystrophy
Metachromatic leucodystrophy
Vanishing white matter disease
Alexander's disease
Canavan's disease

Other
Tumour (glioma, lymphoma, metastases)
Mitochondrial disease
Susac's syndrome

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy; SLE, systemic lupus erythematosus.

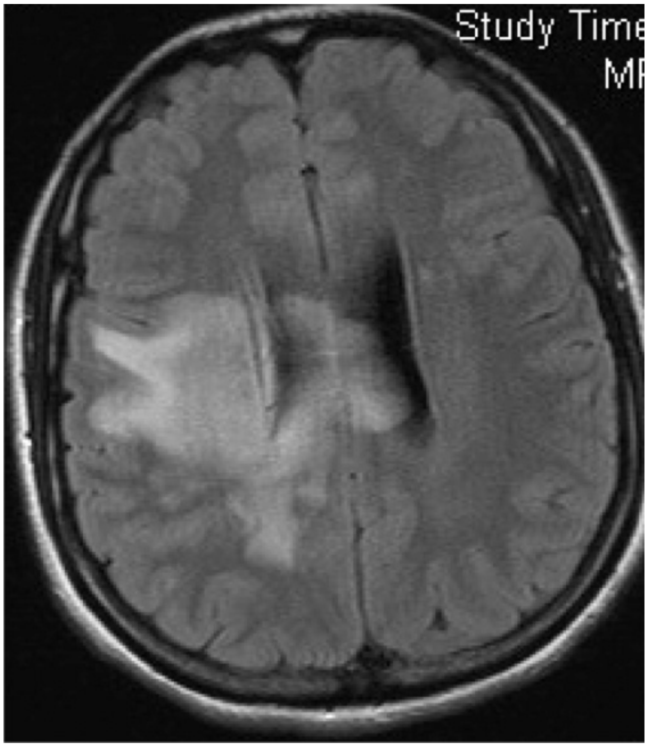


Figure 10.6 Large right temporo-parietal lesion with extension into the splenium of the corpus callosum (MRI T1W axial).

Other multifocal and inflammatory disorders may at times be difficult to distinguish from multiple sclerosis on clinical and imaging grounds: sarcoidosis, systemic lupus erythematosus (SLE), Sjögren's syndrome, Behçet's disease, CNS vasculitis, acute disseminated encephalomyelitis (ADEM) and neuromyelitis optica (NMO). There are some distinctive imaging findings, e.g. meningeal enhancement in sarcoidosis; multifocal, punctate and peri-vascular enhancement in CNS vasculitis; extensive brainstem lesions in Behçet's disease; monophasic disease activity in ADEM, with partial and sometimes marked resolution at follow-up; extensive longitudinal cord lesions in ADEM and NMO. Numerous other non-inflammatory white matter disorders may also enter the differential diagnosis, e.g. progressive multi-focal leucoencephalopathy, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL). In leucodystrophies (e.g. Krabbe's disease, adrenomyeloneuropathy) or metabolic disorders such as phenylketonuria, the white matter abnormalities are typically symmetrical. Rarely, demyelinating lesions may manifest as a single, large or tumefactive lesion within a cerebral hemisphere mimicking a cerebral tumour (Figure 10.6). These lesions tend to be extensive but circumscribed with little mass effect or vasogenic oedema and there may be pathological ring enhancement; however, these lesions appear to resolve rapidly with corticosteroid therapy.

Conventional MRI is relatively insensitive to cortical grey matter lesions and abnormalities in NAWM that are nevertheless abundant in multiple sclerosis. These pathological changes can be detected using more sophisticated imaging techniques. Quantitative MRI abnormalities have been demonstrated in NAWM and include decreased magnetization transfer ratio, increased T1 relaxation time, increased mean diffusivity and decreased

N-acetylaspartate on spectroscopy. While the development of techniques to better detect and quantify these more extensive abnormalities may have some diagnostic role in future, the greater importance seems likely to be in understanding pathogenic mechanisms and assigning prognosis.

Cerebrospinal fluid

When both clinical and imaging features are characteristic for multiple sclerosis, many neurologists will not feel that a lumbar puncture is required, although there are some geographical variations in practice. In those regions where Lyme disease is common, exclusion of this treatable condition warrants a lumbar puncture in almost all suspected multiple sclerosis cases (however, it should be noted that the usual clinical features of neuroborreliosis – facial palsy and meningoradiculitis – are not a common presentation for multiple sclerosis). In clinically definite multiple sclerosis, intrathecally synthesized oligoclonal immunoglobulin G (IgG) bands are found in approximately 90% of patients. A parallel blood sample is required to demonstrate the intrathecal origin of bands as the passive transfer of bands from the systemic circulation has no diagnostic value. Isoelectric focusing and immunodetection of oligoclonal bands is the gold standard technique to provide evidence of intrathecal antibody synthesis (Plate 10.2). A raised IgG index may be informative but is not as sensitive or specific. About two-fifths of patients have a mildly raised CSF white cell count (5–50 mononuclear cells/mm^3) and protein.

Oligoclonal bands occur in other CNS inflammatory disorders including infections (e.g. neurosyphilis, subacute sclerosing panencephalitis [SSPE], neuroborreliosis, human T-lymphocyte virus type 1 [HTLV-1] associated myelopathy and CNS varicella zoster), vasculitis, collagen-vascular disorders and paraneoplastic disease but they are less common in neurosarcoidosis, Behçet's disease and NMO. Whereas in multiple sclerosis the antigenic specificity of the bands is largely unknown, in SSPE and varicella zoster they are largely directed against measles and herpes zoster antigens, respectively.

Laboratory procedures for optimal CSF examination in suspected multiple sclerosis have been defined recently by an expert international panel. Some new laboratory methods for detecting oligoclonal bands, including IgM bands, have been investigated and suggested as being more sensitive and specific in diagnosing and predicting the course of multiple sclerosis. More extensive studies are required to determine their clinical utility.

Evoked potentials

For 10–20 years prior to the widespread introduction of MRI, evoked potentials were important and frequently used diagnostic investigations. Their role was similar to MRI: detection of clinically silent CNS white matter lesions. Because they are less sensitive in this respect than MRI, they are not often requested as part of contemporary diagnostic work-up. The most useful of these investigations is the visual evoked potential; the demonstration of a markedly delayed P100 wave of normal amplitude provides strong evidence for optic nerve demyelination (Figure 10.7). It may still be useful in supporting the diagnosis, especially when the clinical syndrome is in the spinal cord or brainstem and MRI is normal or shows only minor non-specific abnormalities or is obtained in an older age group where the specificity of white matter abnormalities is less. Brainstem auditory evoked potentials and somato-sensory evoked potentials are generally less useful, although may sometimes have a role in establishing the nature of a lesion.

Autoantibodies

No autoantibody has been confirmed to be diagnostic for multiple sclerosis to date. A recent study of CIS patients – who also

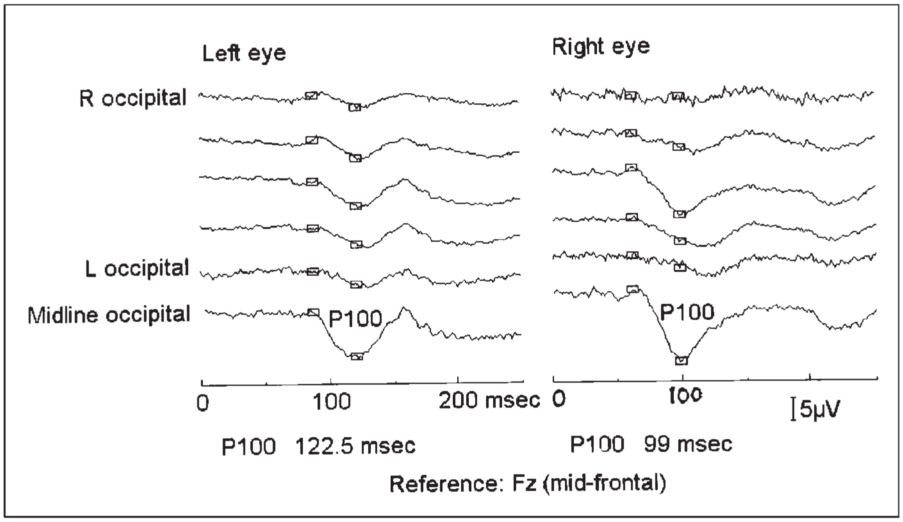


Figure 10.7 Visual evoked potential in left optic neuritis: delayed P100 waveform from left eye; normal response from right eye.

had MRI abnormalities and CSF oligoclonal bands indicating a high likelihood for multiple sclerosis – reported that the presence of antimyelin antibodies in serum substantially increased the risk for developing clinically definite multiple sclerosis. However, several subsequent studies have been consistently negative, reporting as high a frequency of such antibodies in healthy controls or in non-converting CIS patients as in those who develop multiple sclerosis. There is at present no serological test that is of diagnostic value for multiple sclerosis.

Diagnostic criteria

Diagnostic criteria for multiple sclerosis have evolved over recent decades with the emergence and widespread availability of newer laboratory investigations that improve the accuracy of diagnosis, and allow it to be made earlier. However, an incontestable core requirement of all the criteria is objective clinical evidence for a disease affecting CNS white matter. Multiple sclerosis cannot be diagnosed in an asymptomatic individual based on MRI findings alone. The criteria also require evidence that the CNS white matter disorder is disseminated in space and time; where they vary is that the early criteria required clinical evidence for dissemination, whereas more recent criteria allow MRI evidence of dissemination.

Schumacher criteria

The diagnostic criteria of Schumacher *et al.* (1965) were an attempt to logically integrate dissemination in space and time. Definite cases of multiple sclerosis were classed as having objective clinical evidence for disease affecting two or more regions of CNS white matter (dissemination in space), and occurring in episodes lasting at least 24 hours and separated by at least 1 month or with progression over 6 months (dissemination in time), in a person aged 10–50 years at onset and in whom no better explanation could be found by an experienced clinician. This clinically based description remains useful today, and while more detailed aspects of clinical, imaging and CSF findings should be appropriately focused on, one should always keep in mind the caveat 'there is no better explanation'.

Poser criteria

The Poser criteria (1983) retained the concept of at least two relapses with signs of a corresponding CNS white matter lesion in two or more locations as the basis for diagnosing clinically definite multiple sclerosis. They introduced laboratory features to strengthen the diagnostic classification in patients in whom clinical evidence suggested probable or possible multiple sclerosis but was insufficient to be certain, e.g. a patient with two relapses and clinical signs of one lesion could, with additional clinically silent MRI lesions or evoked potential abnormalities, be considered as definite multiple sclerosis. The Poser criteria gave particular weight to the evidence provided by CSF oligoclonal bands indicating an immunological disorder of the CNS. Thus, a patient with two relapses and signs of single CNS lesion plus unmatched CSF oligoclonal bands was classified as laboratory supported definite multiple sclerosis.

McDonald 2001 criteria

The major change in practice leading to further revisions of the Poser criteria was the widespread use of MRI and the emerging evidence that certain imaging features were suggestive of multiple sclerosis. In particular, Barkhof and Tintore had shown that in patients with CIS, three or four of the following brain MRI features had a high specificity for developing clinically definite multiple sclerosis:

1. ≥9 T2 or ≥1 gadolinium enhancing lesions;
2. ≥3 periventricular lesions;
3. ≥1 juxtacortical lesions; and
4. ≥1 infratentorial lesions.

The International Panel that developed the McDonald 2001 diagnostic guidelines adopted the Barkhof–Tintore criteria as evidence for dissemination in space with the modification that one cord lesion could substitute for one brain lesion. The Panel also proposed an alternative, non-evidence based criterion for dissemination in space: two T2 lesions and the presence of CSF oligoclonal bands. They also had a complex MRI requirement for dissemination in time, erring on the side of caution, defined as either a gadolinium-enhancing lesion occurring at least 3 months after the clinical onset or a new T2 lesion shown to have developed more than 3 months after clinical onset. It was thus possible, for the first time, to use imaging evidence for dissemination in space and time to diagnose multiple sclerosis in patients with a single clinically manifest CNS lesion (CIS).

McDonald 2005 criteria

The 2001 criteria were criticized by some as being too liberal – the argument being that anything other than clinically definite mutiple sclerosis would run the risk of false positive diagnoses – and by others as being too conservative – the argument being that because CIS patients with multiple MRI lesions have a high likelihood of developing clinically definite multiple sclerosis, they may as well be diagnosed as multiple sclerosis at presentation.

When the 2001 criteria were applied to two natural history cohorts that had been recruited with a CIS, from specialist centres, and were being followed up with serial clinical and MRI evaluation, they were found to have a high specificity and positive predictive value for development of clinically definite multiple sclerosis over the next 3 years. However, sensitivity of the early dissemination in time criterion – a gadolinium-enhancing lesion after 3 months – was low. One study reported that allowing a new T2 lesion at 3 months of follow-up (many of which must have occurred within 3 months of clinical onset) increased sensitivity without compromising specificity. The substitution of a single spinal cord lesion for a brain lesion had a negligible effect on performance of the criteria in patients with isolated optic neuritis, although substituting all visible cord lesions for an equivalent number of brain lesions considerably increased sensitivity of the Barkhof–Tintore criteria for dissemination in space in patients at the time of multiple sclerosis diagnosis.

A reconvened International Panel in 2005 made revisions to the MRI criteria for dissemination in space and time. These allow any number of cord lesions to substitute for a brain lesion, and a gadolinium-enhancing cord lesion to substitute for an enhancing brain lesion. They also allow for any new T2 lesion occurring more than 30 days after clinical onset to constitute evidence for dissemination in time. The criteria affirm that there must be objective clinical evidence for a CNS lesion, i.e. an abnormality on neurological examination. A suggestive symptom alone (e.g. Lhermitte's symptom) was considered insufficient.

Preliminary application of the 2005 criteria to a multicentre European CIS cohort suggests that they retain a high overall specificity, and that dissemination in time is more specific than dissemination in space per se. In summary, the McDonald 2005 criteria perform well in patients with typical CIS presentations; they have yet to be tested in cohorts who present with an atypical CIS or who have other diseases that are in the differential diagnosis of relapse onset multiple sclerosis.

Diagnostic criteria for primary progressive multiple sclerosis

The diagnosis of primary progressive multiple sclerosis can be problematic. The differential diagnosis is different from relapse onset presentation: it is, most often, the differential diagnosis of a progressive spastic paraplegia or a progressive brainstem/cerebellar syndrome, in order the two most common presentations of primary progressive multiple sclerosis. Experience with the performance of MRI, evoked potentials and/or CSF findings in two large cohorts with a diagnosis of primary progressive multiple sclerosis has helped to inform diagnostic guidelines. The McDonald 2005 criteria for primary progressive require that there has been a progressive CNS syndrome for at least 1 year, and two of three of the following:

1 ≥ 9 T2 brain lesions or ≥ 4 brain lesions plus abnormal visual evoked potentials;

2 ≥ 2 T2 spinal cord lesions;

3 CSF oligoclonal bands.

There should be no better explanation and in patients with a progressive myelopathy, an alternative structural disorder of the cord should always have been excluded by spinal MRI (Table 10.4).

Differential diagnosis

The differential diagnosis of multiple sclerosis is wide and a myriad of neurological disorders may mimic the varying manifestations of the condition. The differential diagnosis can be considered in terms of diseases that cause:

1 A single episode of neurological disturbance which may be focal involving a single site, e.g. optic nerve or spinal cord, or multi-focal;

2 Relapsing neurological disturbance which may be focal or multi-focal; or

3 Progressive neurological disturbance which may be focal or multi-focal.

The differential diagnoses of some of the most common presentations are given in Tables 10.3–10.7, although such lists are necessarily selective and incomplete.

Table 10.4 Differential diagnosis of a progressive spinal cord syndrome.

Tumour
Intramedullary – glioma, ependymoma
Intradural – meningioma, neurofibroma
Extradural – metastasis

Compression (non-tumour)
Vertebral spondylosis/disc prolapse/collapse
Arnold–Chiari malformation

Inflammatory
Multiple sclerosis
Vasculitis
Neurosarcoidosis

Infectious
HTLV-1
HIV
Syphilis
Schistosomiasis
Tuberculosis
Brucellosis

Metabolic
Vitamin B_{12} deficiency
Copper deficiency
Phenylketonuria
Vitamin E deficiency
Cerebrotendinous xanthomatosis

Degenerative
Amyotrophic lateral scelerosis
Primary lateral sclerosis

Vascular
Dural arteriovenous malformation
Cavernous haemangioma

Paraneoplastic

Hereditary
Hereditary spastic paraplegia
Adrenomyeloneuropathy
Friedreich ataxia

Toxic
Nitrous oxide
Lathyrism

The diagnostic process

It is important that the diagnostic process is centred on the needs of the individual with multiple sclerosis. The diagnostic phase is an anxious time, and delay in diagnosis and poor communication is a common cause for complaint. People want a clear and accurate diagnosis and access to appropriate support and information. National guidelines make recommendations for best practice during the diagnostic process (Table 10.8). However, there is still wide variation in the services provided throughout

Table 10.5 Differential diagnosis of optic neuritis.

Anterior ischaemic optic neuropathy
Temporal arteritis
Vasculitis
Sarcoidosis
Neuromyelitis optica
Chronic relapsing inflammatory optic neuritis
Syphilis
Viral infection
Leber's hereditary optic atrophy
Compression/tumour
Raised intracranial pressure
Vitamin B_{12} deficiency
Tobacco-alcohol amblyopia
Susac's syndrome
Neuroretinitis
Eales' disease
Central serous retinopathy
Paraneoplastic optic nerve/retinal disease

Table 10.6 Differential diagnosis of an acute spinal cord syndrome.

Spinal cord compression
Transverse myelitis
Clinically isolated syndrome suggestive of multiple sclerosis
Acute disseminated encephalomyelitis
Neuromyelitis optica
Acute necrotizing myelitis
Infectious (viral, tuberculosis, syphilis, fungal, parasitic)
Vasculitis
Sarcoidosis
Vascular
Spinal cord infarction
Spinal cord haemorrhage

Table 10.7 Differential diagnosis of relapsing CNS neurological disturbance.

Vascular disease
Recurrent transient ischaemic attack/stroke
CADASIL
Congophilic amyloid angiopathy
Fabry's disease
Antiphospholipid syndrome
Vasculitis
Primary angiitis of the CNS
Systemic lupus erythematosus
Sjögren's syndrome
Behçet's disease
Sarcoidosis
Susac's syndrome
Mitochondrial disease
MELAS
Chronic infections
Lyme's disease
HIV encephalitis
Syphilis
HTLV-1
Subacute sclerosing panencephalitis
Whipple's disease
Brucellosis
Fungal/parasitic infections
Migraine
Migraine aura
Familial hemiplegic migraine
Epilepsy
Focal seizures
Todd's paresis

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy; MELAS, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes; HTLV, human T-lymphocyte virus.

Table 10.8 The diagnostic process. Management of multiple sclerosis in primary and secondary care. (NICE 2003.)

An individual who is suspected of having MS should be referred to a specialist neurology service, and seen rapidly within an audited time (will vary according to clinical need but should be no longer than 6 weeks)
An individual should be informed of the potential diagnosis as soon as a diagnosis of MS is considered likely, before undertaking further investigations
Throughout the diagnostic process, the health care professional should: • Find out what and how much information the individual wants to receive • Discuss the nature and purpose of all investigations
The individual should be seen again after all investigations have been completed (recommended within a further 6 weeks) and the diagnosis confirmed or refuted. If the diagnosis is confirmed the individual should be told the diagnosis by a doctor with specialist knowledge of MS; this will usually be a consultant or an experienced specialist registrar
Following diagnosis the individual should be: • Offered at least one more appointment in the near future (recommended in no longer than 4 weeks) to see wherever possible the doctor who gave the diagnosis • Put in touch with a skilled nurse or support worker, ideally with specialist knowledge of MS • Offered written information about disease-specific support organizations • Offered information about the disease specific to the newly diagnosed
Within 6 months of diagnosis, the individual should be offered the opportunity to participate in an educational programme to cover all aspects of MS

the UK and diagnosis often occurs in a random and unsupported manner. This may be partly explained by the over-stretched medical services, but forward planning and reorganization of services may address this problem. There is some evidence that a coordinated diagnostic clinic facilitates an efficient, supportive and cost-effective setting to manage the diagnostic phase. However, the diagnostic model will depend on the locally available expertise and resources. The clinical nurse specialist has been a key development in recent years and is well placed to facilitate the diagnostic process.

Management

In recent years, clinical guidelines have been published that aim to improve the standards of care provided to people with multiple sclerosis. Health and social care professionals involved in the care of people with multiple sclerosis should be aware of current evidence-based practice in order to optimize the standard of management. People with multiple sclerosis should be encouraged to participate fully in decisions on their management. Management requires a comprehensive and multi-disciplinary approach addressing medical, functional, psychological and social aspects of the disease and interventions should be responsive and timely. Management strategies are required to:

1 Provide education and support;
2 Manage acute relapses;
3 Modify the course of the disease; and
4 Treat symptoms and provide rehabilitation.

Education and support

Education and support are an integral part of management from the time of diagnosis and throughout the disease course. Individuals should be provided with information regarding multiple sclerosis, and specific information relating to their disease type and its management. This will facilitate their active participation in their own management. Multiple sclerosis specialist nurses have an essential role in this in the UK, and can provide individualized educational and supportive sessions. Health care professionals work closely with voluntary organizations to provide educational materials such as information booklets, teaching manuals to explain the biology of multiple sclerosis and online decision-making aids for choosing disease-modifying therapies. The Multiple Sclerosis Society in the UK also coordinates educational programmes, such as ‘Getting to Grips’ courses for newly diagnosed individuals.

Management of acute relapses

Management of acute relapses should be comprehensive, addressing all aspects of the relapse. Multi-disciplinary input may be required, particularly if recovery is less than complete. The first step is to assess whether new or increased symptoms are caused by a relapse of multiple sclerosis.

Table 10.9 Assessment of new or increased symptoms and the management of multiple sclerosis in primary and secondary care. (NICE 2003.)

If an individual has a relatively sudden increase in neurological symptoms or disability, or develops new neurological symptoms, a formal assessment should be made to determine the diagnosis (reason for change)

This diagnostic assessment should:

- Be undertaken within a time appropriate to the clinical presentation
- Consider the presence of an acute infective cause
- Involve a GP or acute medical/neurological services

Further neurological investigation should not be undertaken unless the diagnosis of MS itself is in doubt

Asssessment

In the event of new or increased symptoms, people with multiple sclerosis should be able to identify and contact a health care professional who can advise or direct them to the most appropriate local service. National guidelines recommend that a formal assessment should be made to determine the nature of the event (Table 10.9). The possibility of another medical cause for the increase in symptoms must be considered. It is important that an infective cause such as a urinary tract infection, which may be otherwise clinically silent, is excluded. The possibility of dual neurological pathology, e.g. a compressive lesion mimicking a spinal cord relapse, should also be considered. If the new symptoms are thought to be unrelated to multiple sclerosis, access to the appropriate service and treatment should be facilitated.

It is essential that the service provided is flexible and responsive to the unpredictable and acute needs of people experiencing a relapse. The demands on general neurology and medical services often make this difficult. One model to address this issue is to set up a specialist relapse clinic to assess and manage acute episodes. A dedicated telephone line to the specialist service may also facilitate direct access.

Treatment

If a relapse has been diagnosed, treatment to hasten the recovery from the relapse should be considered. Steroid therapy is the only recommended drug treatment. National Institute for Clinical Excellence (NICE) guidelines recommend that steroid therapy should be offered if the relapse causes distressing symptoms or increased limitation of activities.

Steroid therapy

It has been established that steroid therapy may accelerate the recovery from a relapse, although a long-term benefit has not been proven. Its precise mode of action is uncertain but there are several potential mechanisms, including reduction of oedema, stabilization of the blood–brain barrier, reduction of pro-inflammatory cytokines and induction of T-cell apoptosis. Efficacy was suggested in early studies with intramuscular adenocorticotrophic hormone (ACTH), but this practice has been discontinued. Intravenous methylprednisolone, which is now widely used, has been proven to hasten recovery, and to be as effective as ACTH. The comparative efficacy of intravenous and oral steroid therapy has been more contentious. The Optic Neuritis Treatment Trial is the largest study to date to have addressed this issue. This was a randomized placebo controlled study in acute optic neuritis that compared intravenous methylprednisolone, followed by oral prednisone, with oral prednisone alone. Visual recovery was accelerated in the intravenous group, but not in the lower dose oral group. No benefit in long-term visual outcome was seen in either group. An increased rate of new attacks of optic neuritis was seen in the oral prednisone group, and a reduction in the rate of development of multiple sclerosis was reported in the intravenous group at 2 years. However, the beneficial effect of treatment on the development of multiple sclerosis was not sustained at follow-up of 3 years and longer. Comparative studies of intravenous and oral methylprednisolone for acute relapses have shown no clear advantage of intravenous over oral administration, although the studies were small and may have had insufficient power to show a difference. The choice of steroid regimen is variable among neurologists in the UK, but the most popular is intravenous methylprednisolone 1 g/day for 3 days. NICE guidelines recommend intravenous methylprednisolone, 0.5–1 g/day, or high-dose oral methylprednisolone, 0.5–2 g/day, for 3–5 days.

The optimal location for the administration of intravenous steroid therapy is also a source of debate. Intravenous steroids may be administered in hospital as an in-patient or out-patient or at home. Factors that may influence the choice of setting include cost-effectiveness, nursing dependency and patient preference. A Canadian study demonstrated that treatment as an out-patient or at home was more cost-effective than in-patient treatment. A UK study showed that intravenous steroid administration was equally effective and safe and of similar cost in an out-patient and home setting, but coordination of care was better with treatment at home.

Steroid therapy may have side effects and, although their incidence is low, the potential risks as well as benefits should be discussed with the individual. Adverse events from intravenous methylprednisolone in the short-term include taste disturbance, facial flushing, insomnia, psychiatric disturbance, exacerbation of acne and transient hypertension and hyperglycaemia. Steroid therapy may exacerbate infection, which should be excluded before treatment, and urinalysis to rule out urinary tract infection should be performed routinely. Gastrointestinal disturbance, such as peptic ulceration, may be exacerbated. Therefore it is prudent to screen for a history of any other risk factors and cover with a gastric acid inhibitor may be required. Long-term complications are rare with intermittent intravenous steroid therapy, but prolonged courses of oral steroids are more likely to assume the risks of long-term therapy. The relationship between pulsed steroids and osteoporosis has not been established, although osteoporosis may be seen as a result of impaired mobility. Serious complications, such as avascular necrosis, may rarely occur. There is no evidence to guide how frequently it is acceptable to treat with intravenous steroids, but NICE guidelines recommend not more than three courses in a year.

Other therapies

No other immunomodulating therapies are routinely recommended for the treatment of acute relapses. Placebo controlled trials of intravenous immunoglobulin (IVIG) in addition to intravenous methylprednisolone have demonstrated no significant benefit over methylprednisolone alone. A small randomized controlled trial of plasma exchange in patients with acute severe neurological deficits caused by demyelinating diseases, which had failed to respond to steroid therapy, showed improvement in some patients. Plasma exchange may be considered in the event of a catastrophic acute relapse that has not responded to steroid therapy.

Supportive measures

Management of acute relapses should be comprehensive, addressing all consequences of the relapse and not just limited to steroid therapy. Practical supportive measures, such as the provision of care or equipment, may be required. Specific treatment for new symptoms may sometimes be necessary, if the relapse is responding to steroids or improving spontaneously the duration of symptoms may be too short to warrant treatment. Symptomatic treatment may be required for symptoms that persist, or that are distressing even for a short period such as trigeminal neuralgia.

Multi-disciplinary input from neurological rehabilitation services may facilitate the functional recovery from a relapse, and such input should run in parallel with any medical treatment. A randomized controlled trial showed that a multi-disciplinary rehabilitation approach was superior to a standard ward routine in people with multiple sclerosis receiving pulsed intravenous steroid therapy. In-patient rehabilitation may also be beneficial, particularly in people with incomplete recovery from relapses with moderate to severe disability.

Disease-modifying therapy

In the last two decades, a number of therapies have been shown to reduce disease activity in multiple sclerosis, including interferon β, glatiramer acetate, mitoxantrone and natalizumab. This is a major step forward in the management of multiple sclerosis, but it is not without controversy as, although a beneficial effect on relapses has been established, their long-term effects on disease progression and disability are unproven. Furthermore, these treatments are expensive and their cost-effectiveness continues to be a cause for debate.

Currently, interferon β and glatiramer acetate are conventionally used as first line disease-modifying therapy in relapsing remitting multiple sclerosis. Mitoxantrone may be used as induction or rescue therapy in patients with rapidly progressive relapsing remitting or secondary progressive multiple sclerosis. However, the recent licensing of natalizumab marks a new development in disease modification of relapsing remitting multiple sclerosis. It is significantly more effective than conventional disease-modifying therapy, but this is tempered by the rare occurrence of life-threatening adverse events. Within the next few years it is likely that more therapies with superior efficacy, but perhaps also greater risks, will become available. Although this shift to more aggressive management of multiple sclerosis may be daunting, it is just bringing the management approach in line with that of other immune-mediated diseases such as rheumatoid arthritis.

Interferon β and glatiramer acetate

Natural interferon β is a glycosylated protein, synthesized by fibroblasts, that has antiviral, immunomodulatory and antineoplastic effects. The original rationale for its use in multiple sclerosis was based on the hypothesis that the condition is triggered by an underlying viral infection. Although this has not been established as the mechanism of benefit, interferon β was shown to be effective in reducing relapses in multiple sclerosis. The precise mechanism of action of interferon β in multiple sclerosis is unclear and it is likely to involve several different effects that modify the immune response. Relevant immunological effects may include improvement of suppressor T-cell function, increased production of anti-inflammatory cytokines and neutrotrophic and gliotrophic factors, and antagonism of the effects of interferon γ. Interferon β reduces T-cell migration by inhibition of matrix metalloproteinases and down-regulation of adhesion molecules, which may inhibit T-cell migration across the blood–brain barrier. Interferon β also has a direct effect on plasma cells, modulating IgG synthesis, which may stimulate natural interferon production by lymphocytes and inhibit T-cell proliferation.

There are three recombinant preparations of interferon β available: interferon β1b, which is non-glycosylated and differs slightly in amino acid sequence from natural interferon β, and two preparations of interferon β1a, which are glycosylated and identical in sequence to interferon β. They have all been investigated in randomized placebo controlled Phase III trials in relapsing remitting and secondary progressive disease and in clinically isolated syndromes.

Interferon-β1b (Betaferon)

A randomized controlled trial of subcutaneous interferon β1b (250 μg alternate days) in relapsing remitting multiple sclerosis was the first Phase III trial of interferon β to be completed. There was a 34% reduction in annual relapse rate over 2 years, a reduction in relapse severity and an increased proportion of subjects remaining relapse free on treatment. On MRI, there was an 80% reduction in disease activity, as measured by number of active scans and new lesions, and a reduction in lesion load. Interferon β1b has recently also been shown to delay conversion to multiple sclerosis and development of disability in subjects with clinically isolated syndromes.

The effect of interferon β1b in secondary progressive multiple sclerosis has been less clear. A European Phase III trial reported a delay in the progression of disability of 9–12 months over 2–3 years in treated subjects both with and without superimposed relapses. MRI showed a reduction in lesion load and new lesion activity. The clinical results were not reproduced in a North American trial which showed no effect on disease progression, although positive effects were seen on relapse rate and MRI activity. A post hoc analysis attributed this discrepancy to the North American cohort being less clinically active and having fewer relapses.

Interferon-β1a (Avonex)

A Phase III trial of intramuscular interferon β1a (30 μg once weekly) in relapsing remitting multiple sclerosis demonstrated a reduction of relapse rate by one-third in the treated group. The trial was terminated early and in the smaller group of patients who had completed the 2 years of follow-up the reduction in relapse rate was 18%. Time to sustained disability progression was significantly greater in treated subjects. A reduction in enhancing lesions was seen on MRI. Intramuscular interferon β1a has also been shown to delay conversion to multiple sclerosis in clinically isolated syndromes.

Intramuscular interferon β1a (60 μg once weekly) had limited clinical effect in secondary progressive multiple sclerosis in a Phase III trial. A favourable effect was seen on one measure of disability progression, the Multiple Sclerosis Functional Composite, but this was largely because of effects on upper limb rather than locomotor function, and no effect was seen on the EDSS. There was a reduction in relapse rate and MRI lesion activity in the treated group.

Interferon-β1a (Rebif)

A Phase III trial of subcutaneous interferon β1a (22 μg or 44 μg three times weekly) in relapsing remitting multiple sclerosis demonstrated a reduction in relapse rate by 27% in the low-dose and 33% in the high-dose groups over 2 years. Progression of disability was delayed in both treatment arms, with greater delay in the higher dose group. A reduction in active lesions and in lesion load was seen on MRI. Subcutaneous interferon β1a (22 μg once weekly) has also been shown to delay conversion to multiple sclerosis in subjects with clinically isolated syndromes.

In secondary progressive multiple sclerosis, a Phase III trial showed no effect of subcutaneous interferon β1a on progression of disability, although positive effects were seen on relapses and MRI activity.

Side effects of Interferon β

The most common systemic side effect of interferon β is a transient post-dose flu-like reaction with symptoms such as fever, myalgia and headache. These symptoms tend to improve over time and are ameliorated by symptomatic treatment. Injection site reactions are common with the subcutaneous preparations. Abnormalities of liver enzymes and the blood count may occur; although not commonly clinically significant, blood parameters should be monitored. Rarely, an autoimmune hepatitis or thyroid disease may develop and nephrotic syndrome has been reported. An association with depression has been reported, and interferon β may be contraindicated if there is a history of severe depression.

Neutralizing antibodies

Treatment with interferon β is associated with the production of neutralizing antibodies (NAbs), which may reduce or abolish the bioavailability and efficacy of interferon β. The incidence of NAbs in the pivotal relapsing remitting studies at 2 years was 42% with interferon β1b, 24% (22 μg) and 13% (44 μg) with subcutaneous interferon β1a and 22% with intramuscular interferon β1a. Subsequent studies suggest a lower incidence of NAbs for intramuscular interferon β1a. The presence of NAbs has been shown to correlate with reduced clinical, MRI and biological markers of therapeutic efficacy. NAbs cross-react with all preparations of interferon β and so the effects cannot be avoided by switching preparation. Guidelines for NAb testing have been suggested but they are not universally accepted and the the role of NAb testing in routine clinical practice remains unclear.

In summary, interferon β has been proven to reduce relapse rate in relapsing remitting multiple sclerosis by approximately one-third over 2–3 years, and to delay conversion to clinically definite multiple sclerosis in clinically isolated syndromes. Interferon β may reduce accumulation of disability through prevention of relapses but the effect appears modest. Conflicting results have been found in secondary progressive multiple sclerosis, but interferon β does not seem to have a significant impact on progression unrelated to relapses. Open-label follow-up studies have suggested that the benefit from treatment may be sustained, but no controlled studies are available to answer the question of whether interferon β improves prognosis in the long term. Axonal loss, the pathological correlate of disability, may occur from first presentation and so it is suggested that early treatment may have a long-term protective effect but this remains unproven. Currently, there is insufficient evidence to draw conclusions as to the long-term usefulness of interferon β therapy.

Glatiramer acetate (Copaxone)

Glatiramer acetate is a synthetic mixture of polypeptides containing four amino acids. Its exact mechanism of action is not clear but may involve induction of suppressor T cells, major histocompatibility complex blocking and T-cell receptor antagonism. It has also been suggested that its effects may be mediated by brain-derived neurotrophic factor. A randomized controlled Phase III trial of subcutaneous glatiramer acetate (20 mg/day) in relapsing remitting multiple sclerosis demonstrated a 29% reduction in relapse rate in the treated group. Subsequently, a randomized controlled MRI study reported a reduction in enhancing lesions and accumulation of lesion load as well as a reduction in relapse rate. A randomized controlled study of oral glatiramer acetate showed no efficacy. No placebo controlled trials of glatiramer acetate in secondary progressive multiple sclerosis have been reported. A randomized controlled study of oral glatiramer acetate showed no efficacy.

Glatiramer acetate has a favourable side effect profile. A transient acute post-dose reaction with shortness of breath and palpitations may occur. Erythema and lipoatrophy may occur at the injection site, and lymphadenopathy has been reported.

Comparative studies

Comparative studies of different interferon β preparations have been carried out. A prospective study of subcutaneous interferon β1b and intramuscular interferon β1a found interferon β1b to have a superior effect on relapses, disease progression and the development of new lesions on MRI. Subcutaneous interferon β1a (44 μg three times a week) has also been reported to have greater efficacy, as evidenced on relapses and MRI lesion activity, than intramuscular interferon β1a (30 μg once weekly). This seems to indicate that the effects of interferon β are dose-related. This is supported by a study of low-dose subcutaneous interferon β1a (22 or 44 μg once weekly) which showed no significant clinical effect.

The results of a randomized trial comparing subcutaneous interferon β1a and glatiramer acetate have been preliminarily reported to show no significant difference in relapse activity.

Prescribing guidelines

All the interferon β formulations and glatiramer acetate are licensed in the UK for ambulatory individuals with relapsing remitting multiple sclerosis. Interferon β1b is also licensed for secondary progressive multiple sclerosis with superimposed relapses. Prescribing in the UK is subject to strict clinical guidelines, produced by the Association of British Neurologists (ABN), and funding of treatment is governed by the Department of Health's Risk Sharing Scheme. Until recently, disease-modifying therapy was only recommended in subjects with clinically definite multiple sclerosis. In light of the results of the trials in clinically isolated syndromes, the ABN guidelines have been revised to allow early treatment (Table 10.10), but they have not yet been incorporated into the Risk Sharing Scheme. Treatment should be started and supervised by a consultant neurologist, after careful and informed discussion with the individual and, where available, with nurse specialist support.

Discontinuation of treatment

Deciding when to discontinue treatment is a difficult area in which evidence is lacking. The ABN suggest that the loss or limitation of benefit from treatment may be inferred by an increased number and severity of relapses, or the lack of relapse reduction, compared with the pre-treatment 1–2 years, especially if MRI shows new or enhancing lesions and if NAbs (in patients on interferon β) are present in high titre. Furthermore, if relapses are severe and disabling, more aggressive immunomodulation may need to be considered. Discontinuation of treatment should also be considered with the development of non-relapsing secondary progressive multiple sclerosis with the loss of ability to ambulate (EDSS ≥7).

Table 10.10 Updated guidelines for treatment of multiple sclerosis with β-interferon and glatiramer acetate. (ABN 2007.)

All patients should be ambulant (maximum EDSS 6.5) and have a diagnosis of MS established by the McDonald Criteria with relapsing onset

Diagnosis of MS by the McDonald Criteria within 1 year of presentation with a CIS

The rationale for this is that patients with CIS developing MS by the McDonald critera have a high (75–85%) probability of having further relapses within 1 year and developing clinically definite MS within 3 years. Only β-interferon may be prescribed

Relapsing remitting MS with active disease

Active disease is defined as:

1 Two clinically significant relapses in the last 2 years, or
2 One disabling relapse in the last year, or
3 Active MRI scan containing new or gadolinium enhancing lesions that have developed in the last year

Either β-interferon or glatiramer acetate may be prescribed

Secondary progressive MS

Treatment is not recommended in non-relapsing secondary progressive MS and only in relapsing secondary progressive MS when relapses are the predominant cause of increasing disability. Only β-interferon may be prescribed

Primary progressive MS

Neither treatment is indicated

Mitoxantrone

Mitoxantrone is a synthetic antineoplastic agent of the anthracendione family, with broad cytotoxic and immunomodulatory activity. It intercalates with DNA and inhibits DNA repair, and has immunosuppressive effects on proliferating cells, including T cells, B cells and macrophages. It also reduces pro-inflammatory cytokines and induces apoptosis and necrosis of B lymphocytes and monocytes. Two small trials initially suggested efficacy in relapsing remitting and secondary progressive subjects with very active disease, with a reduction in relapse rate and in enhancing lesions on MRI. A pivotal randomized placebo controlled trial of intravenous mitoxantrone (5 or 12 mg/m^2 3-monthly) for 2 years in worsening relapsing remitting and secondary progressive multiple sclerosis showed a significant effect of the higher dose on a multivariate clinical measure, including a reduction in progression of disability and relapses.

Mitoxantrone is a potentially toxic agent. High cumulative doses impair ventricular function and may cause symptomatic cardiac failure. Treatment should not exceed a maximum cumulative dose of 140 mg/m^2 and monitoring of cardiac function is required throughout treatment. Mitoxantrone causes bone marrow suppression and leucopenia and the full blood count should be monitored. Treatment-related acute leukaemia occurs rarely. An incidence of 0.25% has been reported, but this may be higher with longer follow-up. Other side effects include nausea and vomiting, and alopecia, although usually mild. Amenorrhoea occurs in approximately one-quarter of women. It is usually transitory, but it is more likely to be permanent in older women, and women should be counselled regarding the possibility of infertility.

In view of the toxicity of mitoxantrone, its use should be restricted to subjects with aggressive and rapidly progressing disease. It is not licensed for multiple sclerosis in the UK, and there are no national prescribing guidelines. It is usually reserved for people who have failed or are not eligible for conventional disease-modifying therapy. It may be considered if there have been two relapses resulting in residual disability during the previous year, or documented substantial progression in disability over 1 year, and if there are new and enhancing lesions on MRI. Its use in early active disease is being investigated but this is not routinely recommended, although it is sometimes used as induction therapy in aggressive disease. However, its use in relapsing remitting multiple sclerosis is likely to be superseded by natalizumab and other new agents.

Natalizumab

Natalizumab is the first monoclonal antibody to be licensed for use in multiple sclerosis. Monoclonal antibodies are a new class of biological agent designed to interact with specific target antigens and thus have highly selective effects on the immune system. Natalizumab is a recombinant humanized monoclonal antibody directed against α4-integrin, an adhesion molecule that is primarily expressed on T cells. Natalizumab blocks the adhesion of activated T cells with the vascular cell adhesion molecule, expressed on the luminal surface of vascular epithelium, and so prevents activated cells crossing the blood–brain barrier.

A preliminary controlled study of natalizumab demonstrated a dramatic reduction in new enhancing lesions on MRI and in relapse frequency over 6 months. In a Phase III randomized placebo controlled trial over 2 years, natalizumab (300 mg i.v. monthly) reduced relapse frequency by 68%, delayed disease progression by 42% and reduced enhancing lesions by 92%. Natalizumab was generally well tolerated, although 4% of subjects developed a hypersensitivity reaction. Other side effects included fatigue and headache. Persistent anti-natalizumab antibodies developed in 6% of subjects and were associated with a decrease in efficacy.

A randomized controlled trial of combination therapy of natalizumab and intramuscular interferon β1a found superior efficacy compared with interferon β1a monotherapy. However, two subjects on combination therapy developed progressive multifocal leucoencepahalopathy (PML) and one subject died. Another fatal case of PML has occurred during natalizumab treatment for Crohn's disease. Further investigation into the safety of natalizumab has revealed no further cases in over 3000 treated subjects.

In view of the risk of PML, the licence for natalizumab has been restricted. In the UK it is licensed for individuals with rapidly evolving severe relapsing remitting disease, defined as at least two disabling relapses in 1 year and evidence of active disease on MRI. A wash-out period following previous immunosuppression is recommended and monitoring for PML is required.

Alemtuzumab

Alemtuzumab (Campath-1H) is a humanized monoclonal antibody directed against CD52, a cell surface antigen expressed on >95% of T and B lymphocytes, as well as monocytes and macrophages, but not stem cells. Alemtuzumab causes prolonged lymphocyte depletion, including the autoreactive T cells that have a role in the pathogenesis of multiple sclerosis, while there is a reconstitution of B cell numbers over several months. A small study in secondary progressive multiple sclerosis demonstrated a dramatic reduction in relapse rate and enhancing lesions but about half of the subjects still experienced progressive disability and increasing brain atrophy. Initial study in relapsing remitting multiple sclerosis similarly showed a dramatic reduction in frequency of relapses and MRI activity, but there was also a favourable effect on disease progression. Therefore, it has been suggested that therapy may be most effective in early disease. A multicentre rater-blinded study of two doses of alemtuzamab, controlled against high-dose subcutaneous interferon β1a, in early relapsing remitting multiple sclerosis has been reported. Subjects randomized to alemtuzamab were treated with intravenous alemtuzumab (12 mg/day or 24 mg/day for 5 days) at baseline. A further dose (for 3 days) was given at 12 months and, in some patients, at 24 months. At 2-year follow-up there was ≥75% reduction in risk of relapse and ≥65% reduction in risk of sustained accumulation of disability.

Administration of alemtuzumab may cause an acute inflammatory response with pyrexia, malaise and rash, and may transiently exacerbate pre-existing neurological symptoms. Therefore, pretreatment with corticosteroids is recommended. Other adverse effects include infections and autoimmune complications. Autoimmune hyperthyroidism has ben reported in up to one-third of subjects. There is an increased incidence of immune-mediated thrombocytopenia, which may be life-threatening. Alemtuzamab is not currently licensed, but it is likely to be an important treatment in the future.

Other disease-modifying therapies

The following therapies have been investigated in multiple sclerosis, but are not routinely recommended because of insufficient evidence or side effects.

Azathioprine

Azathioprine is a derivative of 6-mercaptopurine and acts as an antimetabolite to decrease DNA and RNA synthesis and therefore lymphocyte proliferation. Several randomized controlled trials of azathioprine have been carried out in multiple sclerosis. A meta-analysis confirmed a slight clinical benefit but debated whether this may be outweighed by side-effects, which include hepatic and bone marrow toxicity. Azathioprine has been reported to be as effective as interferon β in increasing the proportion of patients who remain relapse free at 2 years, but it is not widely used.

Cyclophosphamide

Cyclophosphamide is a cytotoxic alkylating agent with immunosupppressant and immunomodulatory properties. It has been suggested that cyclophosphamide may suppress disease activity in patients with progressive disease, particularly with an active inflammatory component. Most studies have been uncontrolled and no benefit has been demonstrated in small placebo controlled trials. The use of cyclophosphamide is also limited by side effects including leucopenia, bladder toxicity and increased risk of malignancy. A recent systematic review did not support its use in clinical practice.

Hematopoietic stem cell transplantation

Autologous hematopoietic stem cell transplantation has been performed in people with progressive types of multiple sclerosis. A retrospective observational study suggested that the majority of patients clinically stabilized, but the design of the study precluded meaningful interpretation. A mortality rate of 10% was reported.

Intravenous immunoglobulin and plasma exchange

IVIG has been shown to have a beneficial effect on relapse rate and a significant reduction in enhancing lesions has been reported. IVIG is a blood product that is in scarce supply and so, with other agents of similar efficacy available, it is not widely used. A randomized controlled trial of IVIG in secondary progressive multiple sclerosis was negative. Plasma exchange may lead to functionally important recovery in some patients with acute and severe relapses.

Methotrexate

A small randomized controlled trial of low-dose oral methotrexate in progressive multiple sclerosis reported a favourable effect on progression on tests of upper limb function, but there is insufficient evidence to recommend its use.

Negative studies

Many other therapeutic trials have been carried out in multiple sclerosis and failed to show significant benefit. These include trials of hyperbaric oxygen, total lymphoid irradiation, sulfasalazine, oral myelin, anti-CD4 antibody and lenercept (a TNF neutralizing agent). A randomized controlled trial of intravenous cladribine (2-chlorodeoxyadenosine), a purine nucleoside analogue with lymphocytotoxic activity, was negative in progressive multiple sclerosis, although subcutaneous cladribine had a favourable effect in a small trial in relapsing remitting multiple sclerosis.

Future therapies

Monoclonal antibodies

Monoclonal antibody therapies, directed at specific immune targets, are among the most promising therapies for the future.

In addition to those already discussed, rituximab and daclizumab are being investigated. Rituximab is a monoclonal antibody directed against the CD20 antigen, which is expressed on B cells, and it causes depletion of B lymphocytes. Studies of rituximab in relapsing remitting multiple sclerosis, primary progressive multiple sclerosis and NMO are being undertaken. Daclizumab is a monoclonal antibody targeted against the CD25 antigen, the IL2 receptor alpha chain, and its effects are mediated through blocking the expansion of autoreactive T cells. Preliminary studies indicate a reduction in relapses and enhancing lesions, but further investigation is required.

Oral therapies

There is much interest in developing oral disease-modifying agents. Of the agents currently being investigated, FTY720 (fingolimod) appears promising. Fingolimod is an oral immunodulatory agent that is derived from the fungal metabolite myriocin. It is phosphorylated *in vivo* and acts as an agonist of the sphingosine 1-phosphate receptor 1, found on thymocytes and lymphocytes. This results in internalization of the receptor, failure of lymphocyte egress and sequestration of lymphocytes in secondary lymphoid tissues. An exploratory randomized controlled trial of oral fingolimod for 6 months demonstrated a reduction in relapse rate of over 50% and a marked reduction in enhancing lesions. Side effects included nasopharyngitis, dyspnoea, headache, diarrhoea and nausea and one case of posterior reversible leucoencephalopathy occurred. Further evaluation in a Phase III study is awaited. Other oral agents currently being investigated include cladribine, fumaric acid, laquinomod, temisirolimus, teriflunomide and statins.

Neuroprotection and remyelination

Most of the therapies investigated to date have primarily targeted the inflammatory response in multiple sclerosis. However, the role of inflammation in the development of axonal loss and permanent disability is not established and so reducing inflammation alone may not be sufficient to prevent axonal damage. Therefore, it is also important to explore agents that may protect axons and so prevent disease progression. Various neuroprotective agents have been suggested, including glutamate antagonists, sodium channel blockers and cannabinoids. A protective effect of sodium channel blockers has been demonstrated in animal models, and a clinical trial of lamotrigine in secondary progressive multiple sclerosis is underway. A Phase III trial investigating the neuroprotective effects of cannabinoids is being undertaken in primary and secondary progressive multiple sclerosis.

Although it is hoped that the newer therapies, given in early disease, may have a beneficial effect on long-term outcome, therapeutic approaches are still required to address neuronal damage that has already occurred. Strategies to facilitate remyelination and axonal repair are being explored. Such therapeutic approaches include promotion of endogenous remyelination and stem cell replacement therapies. Various growth factors have been explored in animal models, but have not translated into clinical practice. Stem cell replacement therapies may be more promising, although there are a number of obstacles to overcome, not least how to replace cells in a disease that is disseminated throughout the CNS. Therapies may utilize embryonic stem cells or adult stem cells harvested from various sites. Clinical studies of autologous hematopoietic stem cell transplantation have been carried out, as discussed above, but have involved intensive immunosuppression which carries serious risks. A pilot study of autologous bone marrow stem cell therapy is currently underway.

Disease-modifying therapy in primary progressive multiple sclerosis

No treatment has been proven to modify the course of disease in primary progressive multiple sclerosis. Only one Phase III trial, of glatiramer acetate, has been completed to date and this demonstrated no significant clinical effect. Smaller trials of interferon β, mitoxantrone and riluzole have been negative or inconclusive. A Phase III study of rituximab is in progress and a study of FTY720 is anticipated.

Symptomatic treatment

Current disease-modifying therapies have no impact on existing neurological impairment and disability, therefore symptomatic treatment and rehabilitation remain essential elements of management. The evidence base for most symptomatic treatments is at best modest, although national management guidelines provide some limited guidance. Symptomatic management may be challenging as people usually have multiple symptoms or functional deficits. Symptoms should not be considered in isolation, particularly as treatment of one problem may exacerbate or cause another, and management should take a comprehensive approach. This may require input from a wide range of health disciplines and draw on a variety of clinical resources. Routine management may be complemented by specialized multi-disciplinary clinics and in-patient or community-based rehabilitation. Education remains an integral part of management, and an understanding of the basis of an individual's symptoms may facilitate self-management. The management of specific symptoms is now discussed.

Fatigue

Fatigue may be one of the most disabling symptoms of multiple sclerosis. Treatment is difficult and may be unsatisfactory. Any treatable contributory factors such as disturbed sleep patterns because of nocturia or nocturnal spasms and depression should be addressed. Fatigue may be worse after activity and as the day progresses. A fatigue management programme, addressing daily routine and conserving energy, is the mainstay of treatment. Graded aerobic exercise programmes may be helpful. Symptoms may be worse in heat and humidity, which may need to be avoided, and some people may benefit from pre-cooling before undertaking activity. Drug therapy may be considered, although the evidence for efficacy is limited and it is not routinely recommended. Amantadine has been reported to improve fatigue compared to placebo, although the benefit was small. Modafinil, a central stimulating agent, may also improve fatigue in multiple sclerosis. The potassium channel blockers, 4-aminopyridine and 3,4-diaminopyridine, have been proposed to improve fatigue by improving nerve conduction but this has not translated into clinical practice and their use may be limited by side effects. Fluoxetine, a selective serotonin reuptake inhibitor, has been suggested to improve fatigue, but there is little evidence for this in the absence of coexisting depression.

Spasticity

Spasticity may cause stiffness, spasms, pain and contractures and as a result adversely affect mobility, seating, comfort, activities of daily living and care. Management should not primarily aim to abolish spasticity, but rather should be directed to optimize function, alleviate pain and facilitate care. Management incorporates education, physical therapy, drug therapy and occasionally surgery, and a multi-disciplinary approach is usually required. It is essential that any exacerbating factors such as infection, constipation, pain and pressure ulcers are addressed, and it is important to educate the individual or carer to avoid trigger factors. First line treatment is usually physiotherapy which can reduce tone without exacerbating weakness. Review of seating and bed positioning is often helpful. People should be facilitated to continue a home exercise or standing programme, with the help of carers and specialized equipment as necessary. Management should aim to prevent contractures but if they have developed serial plaster casts, removable splints and standing programmes may all have a role in treatment.

Several oral medications may reduce spasticity. Broadly speaking, spasticity is caused by disinhibition of spinal reflexes because of an upper motor neurone lesion and so drug therapies often target spinal pathways. Treatment should start with a small dose and be titrated up slowly until the desired effect is achieved or unacceptable side effects occur, and monotherapy is desirable. The most commonly used agent is baclofen, a chlorophenyl derivative of gamma aminobutyric acid (GABA) and a GABA β-agonist. It acts on pre- and post-synaptic receptors to potentiate spinal inhibition. The most common side effects are drowsiness and muscle weakness, which is particularly unwelcome in multiple sclerosis; large doses may result in CNS and cardiorespiratory depression. Abrupt withdrawal should be avoided as it may cause rebound spasticity, hallucinations and epileptic seizures.

Gabapentin enhances GABA function and has been demonstrated to have a beneficial effect on spasticity in small placebo controlled studies. It is generally well tolerated, although side effects include sedation and dizziness. NICE guidelines recommend baclofen and gabapentin as first line drug agents for spasticity in multiple sclerosis.

Tizanidine acts through its α_2-adrenergic properties resulting in spinal inhibition. Placebo controlled trials of tizanidine have shown it to be effective in reducing spasticity. It has been reported that this is not associated with an increase in weakness, but there is little evidence for this in clinical practice. Side effects include dizziness, drowsiness, dry mouth, fatigue and hypotension. Hepatotoxicity may occur and liver function tests should be monitored during the first few months of treatment.

Dantrolene reduces muscle contraction via the inhibition of calcium release in muscle fibres. It acts peripherally and it can be used as an adjunct to a centrally acting drug. Side effects are common and include nausea, diarrhoea, weakness and fatigue. Irreversible hepatotoxicity may occasionally occur and liver function should be monitored closely. As less toxic drugs have become available, dantrolene is now rarely used.

Benzodiazepines, such as diazepam and clonazepam, reduce muscle tone through augmentation of the inhibitory effects of GABA. The use of benzodiazepines may be limited by their sedative effects but they can be useful as a short-term intervention or for treatment of nocturnal spasms.

Cannaboids have generated much public interest and a beneficial effect on spasticity has been reported in small studies. Their effect is proposed to be mediated through cannabinoid receptors in the CNS. A large randomized controlled trial of cannabis extract and the synthetic cannibinoid, tetrahydrocannibinol, found no benefit on physician-based spasticity measures. There was an improvement in patient-reported spasticity, although this may have been affected by a degree of unmasking. Side effects include dizziness, dry mouth, gastrointestinal disturbance and increased appetite. Cannabinoids are currently not licensed in the UK.

Oral spasticity agents may be limited by systemic side effects, particularly when high doses are required in severe spasticity. Locally administered agents, including intramuscular and intrathecal therapies, may therefore be helpful although they are more invasive. Such treatments should not be performed in isolation, and require a comprehensive approach with specialist multidisciplinary input and monitoring.

Intramuscular botulinum toxin may be useful in the treatment of focal spasticity. It reduces muscle activity through presynaptic neuromuscular blockade. Benefit has been reported in the treatment of distal limb spasticity. It is less helpful with spasticity in large muscles, although it may reduce leg adductor spasticity. Intraneural injection with alcohol or phenol may rarely be used.

For severe generalized spasticity, intrathecal therapies may be considered. Intrathecal administration of baclofen directly targets the spinal receptors that mediate spasticity. Much smaller doses are required than orally and there is a reduction in systemic side effects. The baclofen is administered into the subarachnoid space via a catheter from an abdominally placed subcutaneous pump (Plate 10.3). The pump is externally programmable so that the regime of baclofen can be changed in response to clinical need; this flexibility is vital in a progressive disease such as multiple sclerosis. Long-term studies have indicated that intrathecal baclofen is an effective and well-tolerated treatment of spasticity. However, adverse effects, related to both the implanted device and the dosing, are common and may rarely be life-threatening. Patients must be selected carefully and generally have severe spasticity resulting in severe functional disability or pain that has not responded to oral medication.

Intrathecal phenol may also be an effective treatment for spasticity in a small group of carefully selected patients. It causes indiscriminate nerve destruction, and damage to the sacral nerves may cause bladder, bowel and sexual dysfunction. However, it is a relatively simple procedure and is a useful option in severely disabled patients with existing loss of sphincter function and in whom the more complex treatment of intrathecal baclofen is not feasible.

Aside from intrathecal baclofen pump implantation, surgery has a limited role in the current management of spasticity and techniques such as surgical rhizotomy are now little used. Surgical release of contractures may occasionally be required to improve comfort or function.

Weakness

Treatment for weakness should aim to optimize strength, endurance and function. Therapy-directed exercise programmes, including aerobic training, are the mainstay of treatment. Supportive measures, such as orthoses for focal weakness or specialist seating for postural weakness, should be provided as appropriate. Functional electrical stimulation may be of benefit for foot drop in selected individuals.

Ataxia

Cerebellar ataxia can be an extremely disabling symptom and is an exceedingly difficult symptom to treat. Truncal ataxia may adversely impact on walking, standing and even sitting, and limb tremor and dysmetria may restrict any limb function. Therapeutic options include physical therapy, drug therapy and surgery, although all have limited efficacy. Physiotherapy and occupational therapy are first line interventions and should address posture, seating and aids to improve function and safety. Drug therapy is usually unrewarding. Small studies or ancedotal reports of isoniazid, ondansetron, gabapentin, carbamazepine, propranolol, primidone, clonazepam and levetiracetam provide insufficient evidence to support their use routinely. Stereotactic thalamotomy and thalamic electrostimulation have been reported to be of benefit for tremor in very specific circumstances, although the evidence is limited and the interventions carry significant risks. Neurosurgery may be considered if tremor is severe and intractable.

Bladder and bowel dysfunction

Bladder dysfunction in multiple sclerosis may result from detrusor hyper-reflexia and incomplete emptying. It is important to assess whether incomplete emptying is occurring before initiating treatment as this may be exacerbated by drugs for detrusor instability. This is carried out by measuring the post-micturition residual by ‘in–out’ catheterization or simple ultrasound. If the residual is <100 mL, treatment should be directed at detrusor hyper-reflexia which may be treated successfully with anticholinergic drugs. The most commonly used are oxybutynin, tolterodine and solifenacin. Side effects include dry mouth which may be dose-limiting. In severe cases intravesical therapy may be considered. Intravesical capsaicin has been used to reduce detrusor hyper-reflexia. More recently, detrusor injections of botulinum toxin have been shown to be highly effective for severe urgency and incontinence. If the residual is >100 mL, techniques to manually empty the bladder should be considered. Clean intermittent self-catheterization may be very effective. A bladder stimulator may be tried in ambulatory individuals reluctant to self-catheterize. Desmopressin, intranasally or orally, is an effective and safe treatment for nocturia and nocturnal enuresis. Administered at bedtime it reduces diuresis overnight. It may also be used to reduce daytime urinary frequency, e.g. when travelling, but it must never be used more than once in 24 hours.

If bladder symptoms are not controlled, despite the above measures, further assessment and advice from a specialist continence service should be sought. Supportive measures for urinary incontinence such as reviewing toileting arrangements, and considering a convene drain or pads should be offered. Pelvic floor exercises may be beneficial, especially in women. Education regarding the symptoms of urinary tract infections should be given, and infections should be treated with an appropriate antibiotic. If bladder dysfunction persists after other non-invasive measures have been tried, long-term indwelling catheterization may be considered. Supra-pubic catheterization may be the preferred option, particularly if sexual function is active.

Bowel dysfunction may be less frequent than bladder dysfunction but is still common and may be more difficult to treat. The most common symptoms are constipation, urgency and incontinence. It is important to establish a regular bowel regime and maintaining an adequate fluid intake and increasing dietary fibre may be beneficial. Oral laxatives may be required. Bulk laxatives, such as lactulose, may be helpful in mild constipation. Stimulant laxatives, such as senna and bisacodyl, may be used in more severe constipation. The iso-osmotic laxative polyethylene glycol may be particularly useful. If constipation persists, the use of suppositories or enemas should be considered. Bowel urgency and urge incontinence may be helped by anticholinergic drug therapy. Individuals with faecal incontinenece should be assessed for constipation with overflow.

Sexual dysfunction

Sexual dysfunction is a frequent but often neglected symptom. In males, the most common complaint is erectile dysfunction. Management has improved with the advent of phosphodiesterase inhibitors, such as sildenafil, which should be offered as a first line therapy. If ineffective, intracorporeal therapy with prostaglandin E1 (alprostadil), administered as a urethral pellet, or papaverine may be used. In females, common symptoms include anorgasmia and decreased vaginal lubrication. Lubricants may be helpful, but drug therapy currently has little role. In both sexes any coexistent contributory factors such as depression, anxiety, diabetes, vascular disease and medications should be addressed. Counselling for individuals or couples should also be offered as appropriate.

Pain and paroxysmal symptoms

Pain occurs in the majority of people with multiple sclerosis. It may be neurogenic, as a consequence of direct involvement of central pain pathways, or it may be nociceptive, often musculoskeletal, due to secondary complications of neurological impairment.

Chronic pain is common and includes dysaesthetic extremity pain, painful leg spasms and musculoskeletal back pain. Amitriptyline, gabapentin, carbamazepine, pregabalin and other anticonvulsants may be used for dysaesthetic extremity pain. Painful leg spasms are best managed by treating the underlying spasticity. Musculoskeletal pain may result from abnormal posture and gait; physical therapy input is the first line of treatment, although anti-inflammatory drugs and other analgesics, electrical stimulation and antidepressants may all have a role in treatment. Cannabis extract or synthetic cannabinoids have been reported to improve pain in multiple sclerosis. Although licensed elsewhere, they remain unlicensed in the UK but may be prescribed on a named patient basis. In chronic pain that has not responded to medical treatment, cognitive behavioural therapy may be helpful in selected individuals.

A minority of people have acute and paroxysmal neurogenic pain. Lhermitte's symptom, tonic spasms and trigeminal neuralgia are the most common paroxysmal pains. Carbamazepine and gabapentin may be effective for trigeminal neuralgia and other anticonvulsants, tricyclic antidepressants and misoprostol have been used. Surgery may be considered for intractable trigeminal neuralgia but is less successful than in non-multiple sclerosis related neuralgia; percutaneous procedures may be preferred. Non-painful paroxysmal symptoms may also respond to carbamazepine, gabapentin and other anticonvulsants.

Cognitive and psychiatric dysfunction

Cognitive deficits may have a significant impact on all activities and quality of life. If symptomatic, a formal assessment of cognition should be offered and advice given regarding any implications of the results. In particular, cognitive dysfunction may affect employment and recognition of cognitive deficits may allow adaptations to be made to enable the individual to maintain employment. There is little information available on treatment or rehabilitation of cognitive dysfunction, although retraining of specific attention impairments has been reported to be of benefit in controlled situations. Any other contributory factors such as medication or mood disturbance should also be addressed.

Psychiatric morbidity is increased in multiple sclerosis with mood abnormalities and depression predominating. A lifetime prevalence of depression in multiple sclerosis of approximately 50% has been reported. People with low mood should be screened as to the severity of depression, and referred for specialist psychiatric input if depression is severe. There is a significant increased risk of suicide in multiple sclerosis, and it is important to be vigilant about suicidal ideation. Simple screening tools, such as the Beck Depression Inventory, can easily be incorporated into clinical practice. Contributory factors, such as pain or social isolation, should be reviewed. In mild to moderate depression, counselling and cognitive behavioural therapy may be helpful. Antidepressant therapy is required for some patients but agents with anticholinergic effects may exacerbate bladder and bowel symptoms. Newer agents such as the selective serotonin and noradrenaline re-uptake inhibitors appear to be effective and well tolerated in patients with multiple sclerosis. Emotional lability is helped by tricyclic antidepressants, selective serotonin reuptake inhibitors or behavioural management strategies.

Visual dysfunction

Reduced visual function can occur as a result of optic neuritis, diplopia caused by ophthalmoplegia or oscillopsia from nystagmus. Drug therapy is of no help for permanent deficit from optic neuritis. Gabapentin and memantine have been reported to be of benefit in acquired nystagmus due to multiple sclerosis, but evidence for their effectiveness is limited. Prisms may be of some help in compensating for eye movement disorders. Visual function may also be improved by assessment in a low vision clinic and provision of adaptive equipment.

Vertigo

Giddiness or vertigo occurs acutely as part of a brainstem relapse but can persist. In acute vertigo, often complicated by nausea and vomiting, vestibular sedatives such as prochlorperazine or cinnarizine are useful as well as supportive measures such as bed rest and rehydration. Physiotherapy, including Cawthorne–Cooksey exercises, and appropriate supportive mobility aids, in addition to vestibular sedatives, may have a role in the management of persistent symptoms.

Bulbar and respiratory dysfunction

Dysphagia is a common symptom and patients may most frequently describe choking on fluids or saliva. Assessment by a speech therapist is at the core of management and advice on posture, eating patterns and diet is often helpful. Videofluoroscopy may sometimes be required. In more severe cases, aspiration with the risk of chest infection is a concern and individuals and carers should be alerted to this. Supportive measures such as provision of appropriate seating and chest physiotherapy are valuable but in severe cases percutaneous gastrostomy may be required.

Speech disturbance is usually caused by dysarthria and is not commonly disabling; it is sometimes helped by speech therapy. However, in severe disease, speech occasionally becomes unintelligible or anarthric and communication aids are required.

Respiratory involvement is common but rarely symptomatic in multiple sclerosis. Patients are occasionally aware of disturbances in the rhythm of breathing caused by diaphragm dyskinesia, and even myoclonus, or by central lesions causing abnormal patterns such as apneustic and cluster breathing. More severe involvement may result from acute lesions in the medulla or high cervical cord, and respiratory insufficiency occurs in advanced disease. Early recognition of respiratory complications is important and ventilatory support, including continuous positive airway pressure or non-invasive ventilation, is occasionally necessary.

Temperature sensitivity

Many people report a significant deterioration in function associated with an increase in temperature. Simple advice on heat avoidance, planning of activities around diurnal temperature variation and cooling should be given. Cooling garments may be of benefit for selected people. 4-Aminopyridine has been reported to improve function in patients with temperature sensitivity, although this has not translated into clinical practice and its use is limited by side effects.

Neurological rehabilitation (Chapter 17)

Out-patient and in-patient neurological rehabilitation programmes may be an effective approach to the comprehensive management of many of the problems described above. Although rehabilitation methods have not been evaluated as stringently as pharmacological therapies, there is now evidence to support their use. Randomized controlled studies have shown in-patient rehabilitation reduces disability and improves quality of life in multiple sclerosis. Benefits gained from in-patient rehabilitation may be maintained for several months, but carry-over of benefits declines over time reinforcing the need for continuity of care into the community. However, in the only double-blind controlled trial of in-patient rehabilitation in multiple sclerosis, no significant benefit was reported, although this may reflect methodological issues and highlights the difficulties in evaluating rehabilitation methods. Out-patient multi-disciplinary rehabilitation has also been reported to reduce disability. Physiotherapy alone improves mobility and well-being in multiple sclerosis, with similar effects seen for out-patient and home physiotherapy, although the benefit may only last a few weeks.

In evaluating the efficacy of rehabilitation, it is essential that the outcome measures used are valid, sensitive and reliable. Historically, outcome measures have been developed without the application of rigorous psychometric methods and have been disease-based. More recently, using standard psychometric methods, patient-based measures such as the Multiple Sclerosis Impact Scale (MSIS-29) and the 12-Item Multiple Sclerosis Walking Scale (MSWS-12) have been developed. Preliminary study has shown them to be reliable and responsive, and such measures should facilitate the assessment of rehabilitation in multiple sclerosis.

Symptomatic treatment and rehabilitation in multiple sclerosis is not just limited to addressing physical and cognitive impairments but should encompass the social and psychological needs. The different requirements of people with long-term neurological conditions, including multiple sclerosis, have been set out in the National Service Framework (NSF) for long-term conditions (Table 10.11). Among these requirements, vocational rehabilitation and palliative care are specifically highlighted.

Table 10.11 Quality requirements for the management of long-term neurological conditions. (Department of Health 2005.)

1 A person-centred service
2 Early recognition, prompt diagnosis and treatment
3 Emergency and acute management
4 Early and specialist rehabilitation
5 Community rehabilitation and support
6 Vocational rehabilitation
7 Providing equipment and accommodation
8 Providing personal care and support
9 Palliative care
10 Supporting family and carers
11 Caring for people with neurological conditions in hospital or other health and social care settings

Vocational rehabilitation

Work is a central activity for most adults and contributes to financial and social status. People with multiple sclerosis face restrictions in their ability to work leading to loss of employment. Factors relating to the disease and relating to the job and work environment affect the ability to work. Disease-related factors are not just confined to physical impairments but also include cognitive impairments and fatigue. The need for access to vocational rehabilitation has been highlighted, but specialist vocational rehabilitation services remain scarce. A focus group-based study found that people with multiple sclerosis identified two key needs in the workplace: managing performance and managing expectations. It was suggested that people with multiple sclerosis required support to address the interaction of their impairments, workplace environment and demands of the work, and to provide expert knowledge about employment issues and legislation, and counselling and support to manage complex issues.

Palliative care

Palliative care services have traditionally addressed the needs of people with cancer and terminal illness. In recent years, there has been a shift within these services to also provide support for people with non-terminal long-term conditions. The NSF highlights the need for access to palliative care services for people in the later stages of long-term neurological conditions. Palliative care services have particular expertise in symptom control, provision of social, psychological and spiritual support, and end of life care. This should be multi-disciplinary working across neurology, rehabilitation and palliative care services and staff involved in the care of people with advanced disease should be trained in palliative care skills. A survey of consultants in neurology, rehabilitation and palliative care has found that there is a shortfall in provision of palliative care services, and a lack of coordination between services. Further work is required to develop palliative care services specific to the needs of people with multiple sclerosis.

Complementary and alternative medicine

Use of complementary and alternative medicine in multiple sclerosis is common, with at least one-third of people having tried at least one therapy. Although some therapies have been subject to controlled trials, the evidence base for most therapies is at best limited and insufficient to make definite recommendations. Cannabis has been one of the most extensively investigated therapies, as discussed, and there is limited evidence for nutritional therapies such as linoleic acid. As many people will decide to use complementary and alternative medicine, access to accurate information should be available to assist decision-making. It is particularly important that people are encouraged to evaluate any risks, both financial and health-related. Information is provided by voluntary organizations such as the MS Society and the MS International Federation.

Neuromyelitis optica

NMO (Devic disease) is an inflammatory demyelinating disease of the CNS which is now recognized as being immunologically and pathologically distinct from multiple sclerosis.

Epidemiology and aetiology

NMO typically occurs in young adults (mean age 40), predominantly female (4 : 1). Familial cases have been reported. NMO occurs more commonly in Asian and African populations than multiple sclerosis. It is much rarer than multiple sclerosis in Europe and North America. Optico-spinal multiple sclerosis, a specific variant of multiple sclerosis which is common in Japan, has been found to be associated with NMO-IgG suggesting that it is the same disease as NMO.

An autoimmune basis to this condition was suspected because of the frequent association with connective tissue disorders and auto-immune endocrinopathies (e.g. thyroid, SLE, Sjögren syndrome) and the presence of positive autoimmune serology in a large number of the patients (antinuclear and extractable nuclear antigen [ANA, ENA], antiphospholipid and antithyroid microsomal antibodies).

A new autoantibody, NMO-IgG, has recently been reported in NMO. The target antigen of NMO-IgG is aquaporin-4, a cell membrane water channel important for fluid balance and cell water homeostasis. NMO-IgG has been reported to be 94% specific and 76% sensitive for NMO. It is found in very few patients with classic multiple sclerosis. This specificity suggests a direct pathological role for the antibody rather than a secondary epiphenomenon. Neuropathological data, with the loss of aquaporin-4 in lesions, and a therapeutic response to plasma exchange support the concept that NMO is an antibody-mediated disorder.

Clinical features

The hallmark features of NMO are severe episodes of transverse myelitis and optic neuritis without clinical involvement of other parts of the CNS. There is often a prodrome, with a flu-like illness preceding the symptoms by several days or weeks followed by optic neuritis or transverse myelitis. Simultaneous involvement of the optic nerve and spinal cord occurs in about 10% of patients. Optic nerve involvement may be unilateral or bilateral and is often sudden with complete loss of vision. Bilateral optic neuritis may occur simultaneously or sequentially over a few days. The onset is generally painful with the development of a central scotoma or a peripheral visual field defect and the optic discs appear normal or swollen. Recovery is often less complete than in multiple sclerosis. Myelitis also develops rapidly and is often symmetrical and bilateral, affecting motor and sensory pathways. The myelitis is usually more severe than in multiple sclerosis and often extends over several segments; it often progresses to a severe paraparesis or quadraparesis with loss of bladder and bowel function. High cervical cord involvement may cause respiratory failure. Severe optic neuritis or transverse myelitis should alert to the possibility of NMO rather than multiple sclerosis. NMO may rarely be associated with other neurological features including encephalopathy, focal brainstem signs including ocular and facial palsy, headache, cerebellar ataxia, peripheral neuropathy and tremor.

Investigations

MRI of the spinal cord characteristically shows an intrinsic spinal cord lesion, on T2-weighted imaging, extending contiguously over three or more vertebral segments (Figure 10.8). The acute lesion often occupies the entire cross-sectional area of the affected segments with visible cord expansion, occasionally with cavitation, and intramedullary gadolinium enhancement. This appearance contrasts with multiple sclerosis where partial myelitis is usually associated with small, focal, asymmetrical and often superficial cord lesions rarely extending over more than one segment. Following the acute phase, spinal cord atrophy may develop. MRI brain is classically normal but small non-specific white matter lesions are often present and occasionally multiple sclerosis-like lesions are seen, although usually not fulfilling the Barkhof–Tintore criteria for dissemination in space.

At lumbar puncture the opening pressure is normal. There may be a marked CSF pleocytosis, >1000 cells/mm^3 with severe myelitis, and a cell count >50/mm^3 should alert that the diagnosis may not be multiple sclerosis. A predominance of neutrophils favours the diagnosis of NMO. CSF protein is usually mildly elevated. Oligoclonal bands are rarely present in NMO, occurring in approximately 20–30% of cases and, unlike multiple sclerosis, their presence may be transient.

Pathology

Lesions in NMO show extensive demyelination with necrosis, cavitation and axonal damage. There is perivascular inflammation, with predominant macrophages, granulocytes, eosinophils, complement and immunoglobulin deposition (akin to Pattern II lesions). Loss of aquaporin-4 has been demonstrated in lesions, and it has been suggested that NMO-IgG binding to aquaporin-4 may be the initial event in the development of lesions.

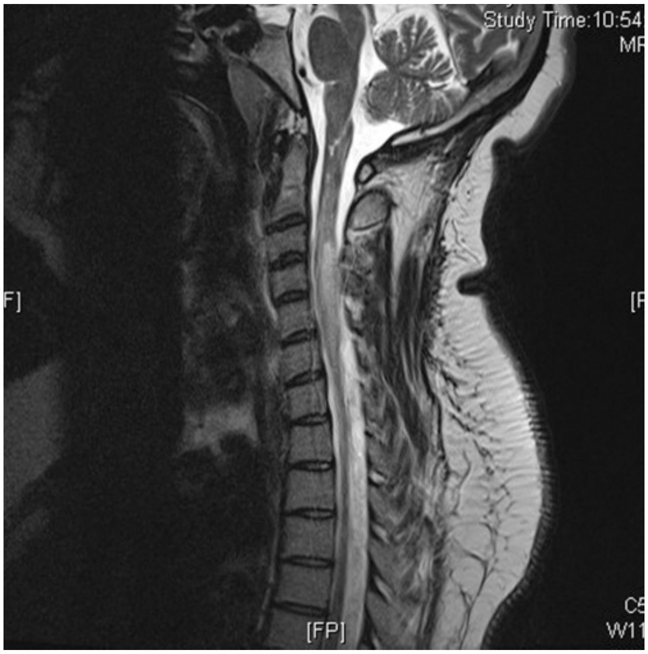


Figure 10.8 Long cervical cord lesion with cord expansion in established neuromyelitis optica (NMO) (MRI T2W sagittal).

Diagnostic criteria

The differential diagnosis of NMO and multiple sclerosis has historically often been difficult. However, diagnostic criteria, incorporating sero-positivity, have recently been revised and are being widely adopted (Table 10.12).

Table 10.12 Criteria for a definite diagnosis of neuromyelitis optica (NMO). (After Wingerchuk *et al.* 2006.)

1 Optic neuritis and acute myelitis
2 At least two out of three supportive criteria:
- Contiguous spinal cord MRI lesion extending over ≥3 vertebral segments
- Brain MRI not meeting diagnostic criteria for multiple sclerosis
- NMO-IgG seropositive status

Symptoms referable to CNS regions other than the optic nerve and spinal cord do not exclude the diagnosis

Course and natural history

NMO is a monophasic or relapsing illness. More than 70% of patients have near or total recovery after the first attack, but even early attacks result in severe and permanent deficits. A rapidly progressive high cervical lesion may result in respiratory failure and complicating sepsis in just a few days. Relapse is common and approximately 55% of patients relapse within 6 months of onset. Poor prognostic factors include female sex, older age, severe myelitis, systemic autoimmunity and a marked CSF pleocytosis. A stepwise deterioration following recurrent attacks may result in a worse natural history than multiple sclerosis. Recurrent attacks of optic neuritis increase the risk of blindness. Recurrent myelitis frequently leads to severe paresis with sphincter involvement, steroid dependency and occasionally requirement of long-term ventilatory support.

Management

Acute attacks of NMO are often severe and necessitate early and aggressive immunomodulation. First line treatment is high-dose intravenous corticosteroids followed by maintenance oral steroids. In patients with acute severe attacks unresponsive to high-dose steroids, particularly if there is incipient respiratory involvement, the next line of treatment is plasma exchange. Efficacy of plasma exchange in NMO has been demonstrated in a small randomized controlled trial. In relapsing NMO long-term immunosuppression is indicated. Azathioprine in combination with oral prednisolone, with a view to tapering the prednisolone, is often used, although there is little evidence base. Experience with other immunosuppressant therapies is limited. A beneficial effect of mitoxantrone has been suggested, but the number of patients studied was small and mitoxantrone cannot be used in the long-term because of the cumulative risk of cardiotoxicity. A benefit has also been suggested from rituximab, which causes depletion of B cells and so may be expected to be useful in a humorally mediated disease, and a controlled trial is underway. There is no evidence to support the use of interferon β or glatiramer acetate. There is a high rate of relapse within the first year in NMO-IgG positive patients and so seropositivity may argue for the introduction of aggressive immunomodulation at initial presentation.

Acute para-infectious inflammatory encephalopathies

Acute para-infectious encephalopathies are typically monophasic encephalitides characterized by multifocal inflammatory lesions, principally affecting the white matter of the CNS. There are two consistently distinguishable pathological subdivisions: acute disseminated encephalomyelitis (ADEM) and acute haemorrhagic leucoencephalitis (AHL).

Acute disseminated encephalomyelitis

ADEM classically occurs in children and young adults. The mean age of onset in paediatric studies is reported as 5–8 years. It typically follows a febrile illness or vaccination by 1–4 weeks, often after the exanthem clears and the initial fever abates. ADEM is most frequently associated with childhood exanthemas particularly measles, rubella and varicella but other infections including mumps, enterovirus, EBV, herpes simplex virus, cytomegalovirus, HHV-6, HTLV-1, adenovirus, influenza A and B, *Mycoplasma*, *Chlamydia*, *Borrelia*, *Listeria*, *Leptospira* and beta-haemolytic streptococcus have all been implicated. Post-vaccination ADEM occurs less frequently. It has been particularly associated with rabies vaccine, notably the Semple neural vaccine, but has rarely been reported with the measles, pertussis, diphtheria, tetanus, rubella, Japanese B encephalitis, typhoid and hepatitis B vaccines.

Clinical features

The onset is usually with a low-grade fever, headache and meningism preceding the development of drowsiness and encephalopathy which may progress to stupor and coma. Neurological deficits are typically multi-focal and include seizures, hemiparesis, paraparesis, ataxia, visual loss, sensory disturbance, dysphasia, cranial nerve palsies, choreoathetosis, myoclonus and sphincter disturbance. ADEM evolves rapidly over hours to days. It is rarely fulminant, with acutely raised intracranial pressure leading to tentorial herniation and death within 72 hours. Respiratory failure resulting from brainstem involvement may also occur. In some patients there is an associated acute psychosis, depression and hypersomnolence. A number of characteristic patterns are seen. Following measles infection, myelitis with hemiparesis or paraparesis is common. Post-rubella ADEM may be associated with seizures, coma and moderate pyramidal signs. Varicella may lead to cerebellar ataxia with a mild pyramidal defect. Rabies vaccination is associated with radicular and peripheral nerve involvement.

Pathophysiology

It is generally accepted that the pathogenesis of ADEM is immune-mediated, rather than caused directly by infection. The exact mechanism of this is not clear. It has been proposed that the preceding infection or vaccine cross-activates an immune reaction to myelin through molecular mimicry. Alternatively, it has been suggested that the inflammatory response to the initial agent results in the activation of pre-existing encephalitogenic T cells.

Pathological examination of the brain in ADEM classically shows multiple peri-venous zones of demyelination in the cerebral white matter. The changes found in patients dying early in the disease affect the small blood vessels of both grey and white matter with hyperaemia, endothelial swelling, vessel wall invasion by inflammatory cells, peri-vascular oedema and haemorrhage all preceding the demyelination. Patients dying later in the disease process show zones of lymphocytic infiltration and demyelination, often with relative axonal sparing – lesions are discrete and surround small and medium size vessels which have peri-vascular pallor. Advanced lesions may show astrocytic proliferation with gliosis and mild meningeal inflammation. The lesions are generally homogeneous in appearance and appear to be of the same age.

Differential diagnosis

ADEM may be difficult to distinguish from the first presentation of multiple sclerosis. A fulminant presentation may also be indistinguishable from AHL. In comparison with multiple sclerosis, ADEM tends to occur in younger patients (mainly children) and it is more common in males. Encephalopathy, headache, fever and a multi-focal presentation are more common, as is a history of a preceding infection or vaccination. Recently proposed diagnostic criteria for ADEM actually require there to be an encephalopathy. Other CNS infections and inflammatory diseases must be excluded, and tumours are in the differential diagnosis of mass lesions.

Distinguishing ADEM from multiple sclerosis may also be difficult if there are further episodes. In an attempt to distinguish ADEM and related disorders from multiple sclerosis, the International Pediatric MS Study Group has recently proposed definitions for the major CNS inflammatory demyelinating diseases including ADEM, although these are not yet validated. The definitions for monophasic, recurrent and multiphasic ADEM are given in Table 10.13.

Table 10.13 International Pediatric MS Study Group consensus definitions for acute disseminated encephalomyelitis (ADEM). (After Krupp *et al.* 2007.)

ADEM (monophasic)

First clinical event with presumed inflammatory or demyelinating cause, with acute or subacute onset that affects multifocal areas of the CNS. Clinical presentation must be polysymptomatic and must include encephalopathy (behavioral change or alteration of consciousness)

Event should be followed by improvement, clinical or MRI, but there may be residual deficits

No history of a prior demyelinating event

No other aetiologies can explain event

New or fluctuating symptoms, signs, or MRI findings within 3 months of the event are considered part of the acute event

Neuroimaging shows focal or multi-focal lesion(s), predominantly involving white matter, without evidence of previous destructive white matter changes

Recurrent ADEM

New event of ADEM with recurrence of initial symptoms and signs, 3 months or more after the first ADEM event, without involvement of new clinical areas

Event does not occur while on steroids, and occurs at least 1 month after completing therapy

MRI shows no new lesions; original lesions may have enlarged

No better explanation exists

Multiphasic ADEM

ADEM followed by a new clinical event also meeting criteria for ADEM, but involving new anatomic areas of the CNS

The subsequent event must occur at least 3 months after the onset of the initial event and at least 1 month after completing steroid therapy

The subsequent event must include polysymptomatic presentation including encephalopathy, with neurologic symptoms or signs that differ from the initial event

The brain MRI must show new areas of involvement but also demonstrate complete or partial resolution of those lesions associated with the first event

Investigations

CSF may be normal in up to 50% of patients but may reveal an elevation in the opening pressure and a mild lymphocytosis (>50/mm^3), although occasionally there may be a polymorphonuclear leucocytosis. The protein is elevated in approximately 50%. Oligoclonal bands may be present acutely in up to 30% of patients but often disappear on repeat testing. CSF polymerase chain reaction (PCR) for viral infection may show the underlying precipitating agent. MRI is most useful in the diagnosis of ADEM, with abnormalities frequently evident on T2-weighted (Figure 10.9) and FLAIR imaging, although MRI may be normal early in the disease. The lesion load is often extensive with large and multifocal lesions, and lesions may be confluent and ill-defined. Lesions are not confined to the white matter but involve the cortical and deep grey matter. Mass lesions, mimicking tumours occur. 'Black holes', hypointense lesions on T1-weighted imaging, are typically absent. Lesions often enhance with gadolinium, reflecting their acute and synchronous development, but enhancement of the meninges is unusual. Spinal cord lesions are often large, extending over several levels, with swelling and mass effect, and have a predilection for the thoracic cord.

Although MRI appearances may be suggestive of ADEM, no features are specific to ADEM. It is not possible to distinguish ADEM from multiple sclerosis on the basis of MRI, although follow-up imaging may be helpful in the differential diagnosis. Brain MRI appearances may normalize in approximately 40% of patients with typical ADEM. The development of new lesions, after an interval of at least 3 months, is inconsistent with a diagnosis of monophasic ADEM.

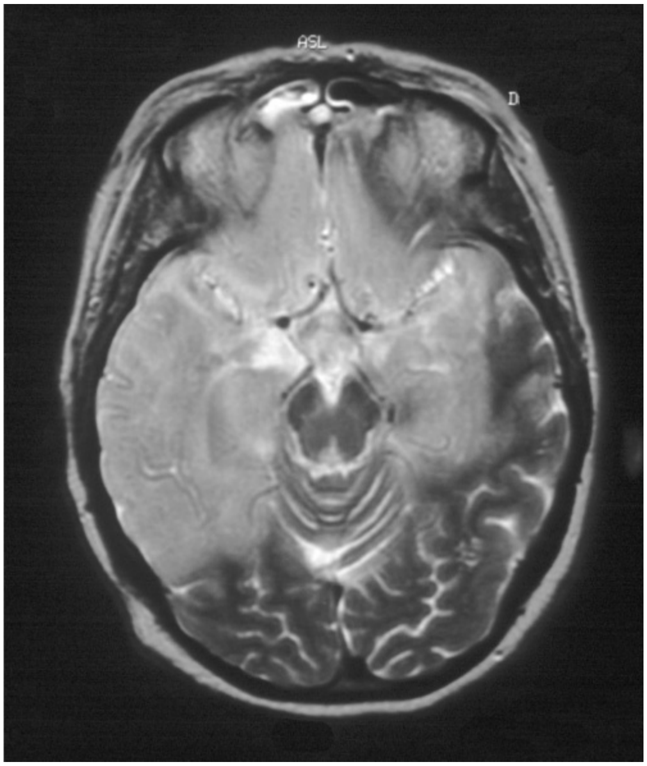


Figure 10.9 Extensive confluent demyelination in acute disseminated encephalomyelitis (MRI T2W axial).

Clinical course and prognosis

ADEM is usually a monophasic illness which is self-limiting. Recovery takes place over weeks to months, and full recovery may occur in about 50–75% of cases. However, major neurological sequelae may occur in up to one-third of patients and mortality is approximately 5%. There appears to be a worse prognosis if seizures and coma accompany the acute illness. Common residual deficits include hemiparesis, ataxia, blindness, cognitive dysfunction and epilepsy. Recurrent or multi-phasic ADEM has been reported in up to 20% of patients but there is debate as to when further events might indicate a relapse of ADEM rather than the existence of multiple sclerosis.

Management

Management involves meticulous support and care, often in an intensive care unit, with adequate hydration and treatment of pyrexia, seizures and raised intracranial pressure. Patients may be given antibacterial and antiviral medication to treat the underlying infection. Empirically, first line treatment for ADEM is usually high-dose intravenous methylprednisolone, for 3–5 days, followed by a tapering course of oral steroid over a few weeks. If unresponsive to steroids, plasmapheresis or IVIG may be considered, although the evidence for these is limited. Rarely, acute cerebral oedema, refractory to conventional management, may require decompressive hemicraniectomy.

Acute haemorrhagic leucoencephalitis

Acute haemorrhagic leucoencephalitis (Hurst's disease) is a severe acute fulminant encephalopathy. There is generally an abrupt onset following an infection and the precipitating symptoms may be masked. Onset is usually between 20 and 40 years but it occasionally occurs in children. It is more common in males. Pathologically it is characterized by a small vessel vasculitis associated with haemorrhage and demyelination.

Clinical features

The course is generally brief and rapid, commonly leading to death. It presents with acute pyrexia, headache, photophobia, meningism leading to progressive encephalopathy with confusion, lethargy and deepening coma over a few days. Focal neurological signs developed. Cerebral oedema usually develops causing tentorial herniation resulting in death.

Investigations

There is marked elevation of the peripheral white cell count and erythrocyte sedimentation rate (ESR). The CSF pressure is raised with a moderately elevated protein level and a polymorphonuclear leucocytosis accompanied by an elevated red cell count and xanthochromia. Glucose levels are normal. Oligoclonal bands are

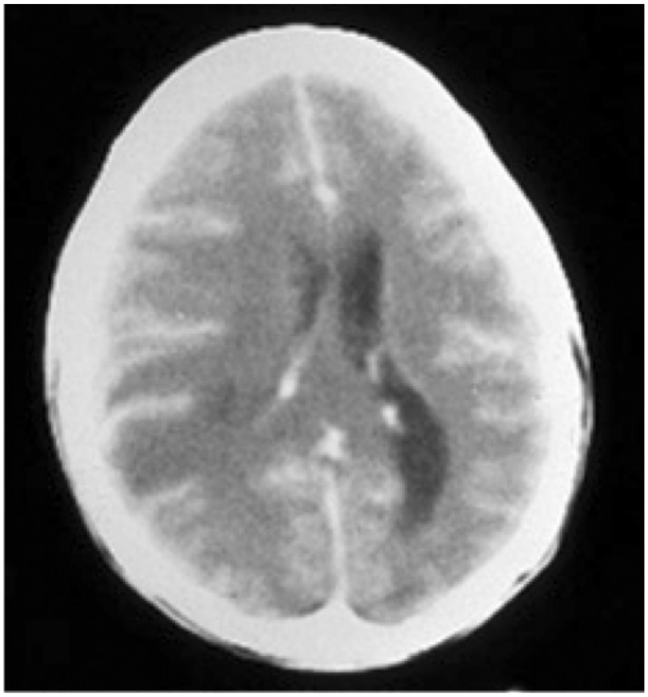


Figure 10.10 Acute necrotizing haemorrhagic leucoencephalitis. Diffuse oedema predominantly in one hemisphere (CT scan).

rarely present. Computed tomography (CT) scan shows diffuse oedema and may show early haemorrhagic change (Figure 10.10), MRI shows numerous and large hyper-intense lesions on T2-weighted imaging. Haemorrhagic change may be seen with subsequent development of necrosis. Electroencephalography (EEG) is abnormal in up to 90% of patients with diffuse slowing, although there may be lateralizing features.

Prognosis

The prognosis of AHL is grave and most patients (up to 70%) die within 1 week of onset. Survivors may have severe residual deficits including seizures, cognitive and psychiatric disturbances. Complete recovery is exceptional.

Management

There is little evidence to guide management but, because of the acute inflammatory nature of the condition, high-dose intravenous steroids are used and plasma exchange and IVIG have also been tried. Surgical decompression may be necessary if severe cerebral oedema develops.

Leucodystrophies

Leucodystrophies are inherited abnormalities of myelin development related to various enzyme defects in lipid metabolism (Chapter 18). The most important conditions are:

- Adrenoleucodystrophy/adrenomyeloneuropathy;
- Globoid cell leucodystrophy;
- Metachromataic leucodystrophy.

Other genetically defined leucodystrophies with autosomal dominant transmission have also been described in the absence of distinct biochemical defects.

Adrenoleucodystrophy and adrenomyeloneuropathy

Adrenoleucodystrophy (ALD) and adrenomyeloneuropathy (AMN) are caused by the presence of very long chain unbranched fatty acids accumulating in many tissues. The genetic defect is in the *ABCD1* gene on Xq28 in which multiple mutations have been described. This gene codes for a peroxisomal membrane protein which facilitates the transport of very long chain fatty acids (VLCFA) or their derivatives into peroxisomes.

Clinical features

The condition may occur in variable phenotypes:

1. Rapidly progressive childhood cerebral form (CCER) of ALD causing profound disability during the first decade;
2. Mild, adult onset AMN with unlimited lifespan;
3. Adrenocortical insufficiency without neurological abnormalities (Addison disease);
4. Adult cerebral forms with psychiatric features;
5. Mild or asymptomatic presentation in female carriers.

Childhood cerebral adrenoleucodystrophy

In CCER, early neurological development is normal and the mean age of onset is approximately 7 years. The initial features are behavioural with hyperactivity and attention deficit. Deterioration of visual acuity and hearing develops with rapidly progressive corticospinal involvement and the development of severe tetraparesis, dementia, seizures and ultimately a persistent vegetative state. Most children die within 2 years of onset.

Adult onset adrenomyeloneuropathy

The mean age of onset of AMN is in the mid twenties with a slowly progressive spastic paraparesis and sensory disturbances most severe in the lower limbs. There is also progressive sphincter disturbance with incontinence and impotence. The condition is slowly progressive over many years although more aggressive forms are occasionally seen. There may be a predominantly demyelinating peripheral neuropathy leading to lower motor neurone weakness of the limbs, reduced reflexes and slowing of nerve conduction.

Pathology

CCER is characterized by a diffuse symmetrical demyelination associated with peri-vascular inflammation and often originating in the parietal occipital region. AMN is caused by a distal axonopathy (dying back) of the long spinal cord tract and peripheral nerves with mild or no inflammatory reaction. Demyelination is secondary to the axonopathy.

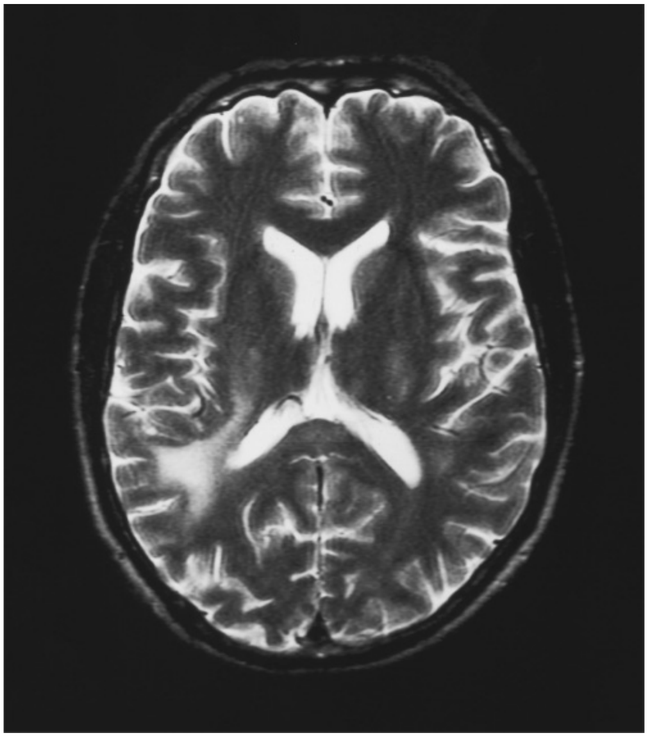


Figure 10.11 Adrenoleucodystrophy (MRI T2W axial).

Diagnosis

AMN can be distinguished from multiple sclerosis by the X-linked inheritance pattern and the presence of symmetrical and contiguous myelin loss with pronounced axonal degeneration and involvement of the adrenal glands. MRI in childhood ALD shows increasing confluent and often extensive abnormality of the cerebral white matter on T2-weighted imaging, with a posterior hemisphere predominance and enhancement particularly at the edges of the lesions (Figure 10.11). Imaging findings are less striking in AMN and can be normal in more than 50% of patients. Asymptomatic mass lesions may rarely be seen. CSF is usually normal or shows only mild inflammatory change and rarely contains oligoclonal bands. The diagnosis depends on the demonstration of increased plasma levels of VLCFA, and can be confirmed by specific genetic testing. Approximately 20% of heterozygous female carriers may develop a mild AMN-like condition but this tends to be of later onset.

Management

Corticosteroid replacement is required if there is adrenal insufficiency. It is necessary to restrict the intake of saturated VLCFA in combination with use of glyceroltrioleate and glyceroltrierucate (Lorenzo oil), although there is little overall effect on the disease load. Bone marrow transplant significantly diminishes plasma VLCFA but clinical results are poor in patients with advanced disease. There is no benefit from immunosuppression but stem cell research may be promising.

Globoid cell leucodystrophy (Krabbe's disease)

Globoid cell leucodystrophy is an autosomal recessive condition caused by a deficiency in lysosomal enzyme galactocerebrosidase which leads to an accumulation of psychosine and galactocerebroside. There is no lipid accumulation in the CNS except in the microglia and macrophages (globoid cells) and it is the toxic effect of psychosine on oligodendrocytes that is responsible for myelin dysgenesis. The gene for galactosylceramide galactoside lies on chromosome 14 and more than 60 mutations have been identified.

Clinical features

Onset is usually in infancy (<6 months in 80%) but juvenile and adult forms are described. The initial manifestations are irritability with tonic spasms and early peripheral nerve involvement. There is progressive regression in motor development with increase in tone, opisthotonus and decerebrate posturing. The condition is associated with optic atrophy and blindness. In the most aggressive forms there is inevitable progression to death over a few years.

In the late infantile form (onset 2–4 years) there is initially normal cognitive function but progressive ataxia and spastic paraparesis develop with subsequent optic atrophy, dysarthria and cognitive and behavioural regression. The juvenile and adult forms have a more slowly progressive spastic tetraplegia, optic nerve pallor and a sensori-motor demyelinating peripheral neuropathy with pes cavus.

The pathology is characterized by a severe loss of oligodendroglia, myelin and axons with dense astrocytic proliferation with the presence of globoid cells and loss of myelin in the peripheral nerves.

CT shows hypodensity in the white matter, particularly in the parieto-occipital region but also involving the brainstem and cerebellum. MRI confirms decreased T1 and normal or increased T2 signal causing symmetrical plaque-like abnormalities in the hemispheres, sometimes predominantly affecting cortico-spinal tracts. The CSF often shows elevated protein but a normal cell count. There is slowing of nerve conduction velocity consistent with a demyelinating neuropathy.

Treatment is symptomatic although bone marrow transplant has been of some benefit in juvenile forms. The prognosis for this condition is variable and prolonged survival does occur.

Metachromatic leucodystrophy

Metachromatic leucodystrophy (MLD) is an autosomal recessive condition brought about by reduced activity of arylsulphatase A (ASA) which causes degredation and accumulation of sphingolipid substrate, cerebroside-3 sulphate (galactosylsulphatide). ASA activity is encoded by a gene on chromosome 22q13 and over 60 mutations have been identified. The abnormal metabolite accumulates in various tissues and cells including oligodendrocytes, Schwann cells, neurones and retinal ganglion cells as well as hepatic, splenic and renal cells. Galactosylsulphatide is a significant component of myelin and the abnormal metabolism leads to profound functional impairment of oligodendrocytes and Schwann cells causing demyelination in the central and peripheral nervous systems.

Clinical features

The condition exists in three forms:

1 Early onset (1–2 years);
2 Juvenile (3–16 years); and
3 Adult (>16 years).

Early onset MLD

This is the most frequent form of the condition, presenting with rapid cognitive and motor deterioration manifest as ataxia and spastic paraparesis culminating in prolonged coma, persistent vegetative state and death. In the infantile form, bone marrow transplants can stabilize or lead to slow progression of the CNS disease but rarely affect the neuropathy. A late infantile form (second year of life) presents with the regression of motor milestones and instability of gait leading to flaccid weakness and hypotonia. There is cognitive regression, bulbar weakness and progressive quadriplegia leading to persistent vegetative state.

Juvenile MLD

The juvenile form is associated with cognitive and behavioural disturbances leading to impaired school performance and occasional confusion. Focal neurological features develop later in the course of the disease with a progressive gait disturbance, dysarthria and extrapyramidal dysfunction which progresses steadily but more slowly to severe impairment.

Adult MLD

The adult form causes behavioural disturbance with change in personality, impairment of academic performance and progressive anxiety, memory disturbance and emotional lability. There may be secondary depression with a schizophrenic psychosis and paranoid delusions. There is an associated demyelinating peripheral neuropathy. Progressive bulbar and spastic limb weakness leads to a decorticate state usually associated with optic atrophy. Progression may continue for up to 10 years before death. Systemic features are also seen.

Pathology

The main pathological feature of MLD is demyelination with the deposition of metochromatic granules in both central and peripheral nervous systems. There is an accumulation of sulphatide which is the characteristic pathognomonic feature of MLD.

Investigations

T2-weighted MRI shows diffuse extensive symmetrical hyperintense signal in both the peri-ventricular and subcortical supratentorial anterior white matter with sparing of the arcuate or U fibres (Figure 10.12). Nerve conduction studies show a demyelinating peripheral neuropathy. The diagnosis can be made by a direct analysis of ASA and management requires various dietary regimes and symptomatic care. Carrier identification may be achieved by assay of ASA.

Management

Management requires various dietary regimes and symptomatic care. Bone marrow replacement in selective patients may be of value early in the course of the disease.

Pelizaeus–Merzbacher disease

Pelizaeus–Merzbacher disease (PMD) is an X-linked defect causing a mutation in a protein component of myelin and leading to dysmyelination. In the connatal form of PMD, symptoms develop in the neonatal period with severe progressive motor and

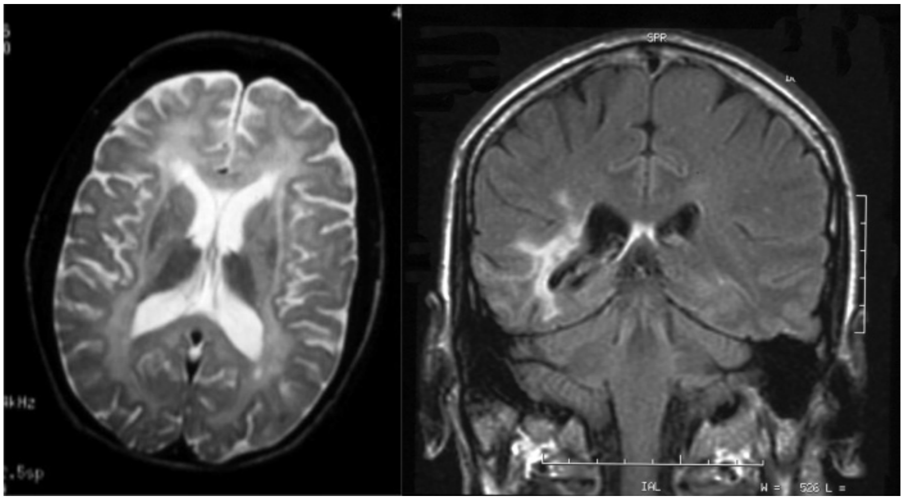


Figure 10.12 Metachromatic leucodystrophy. (a) MRI T2W axial. (b) MRI T2W coronal.

cognitive impairment and seizures. The children have neonatal nystagmus, impaired expressive language and an inability to hold the head erect. There is laryngeal stridor, progressive ataxia and spasticity and most children are never able to walk. The classic form of PMD is less aggressive with symptoms coming on between 1 and 5 years with progressively impaired gait resulting from spastic paraplegia. In adults there may be a pure uncomplicated spastic paraplegia type 2 (SPG2) but nystagmus and visual impairment may occur. Progression is slow but most patients become wheelchair-bound. PMD is caused by a mutation on chromosome Xq22 in the gene coding for protein lipoprotein (PLP) which is expressed in both the central and peripheral nervous systems. The connatal form is usually caused by missense mutations. PLP is composed of approximately 50% of myelin protein and therefore the condition is associated with a severe reduction or absence of myelin, causing oligodendrocyte death or dysfunction.

MRI of the brain shows uniform increased intensity of the white matter of T2-weighted images and occasional atrophy is seen. Nerve conduction studies are generally normal although a mild demyelinating neuropathy is associated with mutations or duplication affecting the PLP.

The prognosis of early onset severe connatal PMD is poor, with loss of cognitive impairment leading to a vegetative state and death by the age of 10. Some patients with late onset forms of the condition may be only mildly affected with only slight limitation in life expectancy.

Leucoencephalopathy with vanishing white matter

Leucoencephalopathy with vanishing white matter, also known as childhood ataxia with central hypomyelination, is a rare leucoencephalopathy associated with diffuse loss of cerebral and cerebellar white matter. Early motor and cognitive development is normal but onset is usually before the age of 6. Later onset in childhood, adolescence and adulthood has been described. The condition presents with a rapidly progressive ataxia and spasticity which may be exacerbated following infection or trauma. Optic nerve atrophy and seizures develop before evolution into severe neurological disability and a persistent vegetative state. The condition is relentlessly progressive with death occurring within a few years. In the older onset patients, cognitive deterioration is often prominent and the course of the disease may be less aggressive. Imaging shows diffuse signal hypo-intensity in the hemispheric white matter with bilateral involvement of the long tracts in the pons. Cortical atrophy and ventricular dilatation are usually absent. Pathology is characterized by extensive hypomyelination and rarefaction of the white matter. There is loss of axons but preservation of cortical neurones and no inflammatory features, the white matter shows extensive cavitation and vacuolation with gliosis. The condition appears to be caused by a premature loss of mature oligodendrocytes by apoptosis with a secondary inefficient remyelination. It is an autosomal recessive disorder with an age-dependent penetrance. No effective treatment is available.

Alexander's disease

Alexander's disease is a rare form of leucodystrophy which usually occurs in infancy but rarely may affect juveniles and adults. The condition is caused by a heterozygous dominant mutation in the gene for glial fibrillary acidic protein (GFAP), a protein component of astrocytic intermediate filaments. It is characterized by progressive macroencephalopathy with developmental delay, cognitive impairment, spasticity and seizures. Onset is usually in the first or second year and progression occurs rapidly over 3–4 years. In later onset forms of the condition there may be oculomotor abnormalities, palatal myoclonus and cerebellar symptoms but the predominant manifestation is progressive pseudobulbar and pyramidal tract involvement with spasticity and hyperreflexia. The family history is often more prominent suggesting an autosomal dominant transmission and imaging shows white matter changes predominantly in a fronto-temporal distribution. Pathologically the condition is characterized by diffuse demyelination with Rosenthal fibres. These are cytoplasmic inclusions that occur in astrocytes and are found in a peri-ventricular and subpial distribution. The pathology predominantly affects the frontal lobe but frequently spreads to involve subcortical and arcuate fibres. The diagnosis of Alexander's disease can now be made by genetic analysis for the mutation in GFAP.

Canavan's disease

Canavan's disease is a rare autosomal recessive condition particularly found in the Ashkenazi Jewish population. Onset usually begins in infancy with macrocephaly and progressive delay in development and motor retardation. The disease is aggressive and progresses to seizures and profound hypotonic weakness with gastrointestinal involvement within the first decade. Atypical forms occur with milder manifestations including macrocephaly, developmental delay and retinitis pigmentosa but with a much slower progression into the teens. The condition is brought about by a mutation in the aspartoacylase (ASPA) gene with complete or partial loss of the enzyme activity leading to an accumulation in *N*-acetylaspartic acid in the brain and CSF.

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11

Headache

Peter Goadsby

Headache is a ubiquitous experience, the existence of which can be found in writings from antiquity. It is the most common reason for referral to neurologists in the industrial world, and holds similar prominence in the developing world. This chapter provides a summary of useful points and for more detailed treatment, readers are referred to textbooks listed at the end of the chapter. In recent times, the anatomical and physiological basis has been better understood and there is a growing range of pharmacotherapeutic options particularly for primary headache.

General principles

Headache was revolutionized in a nosological sense by the first edition of the International Classification of Headache Disorders, which has now been revised (Headache Classification Committee of the International Headache Society [IHS], 2004). The author will largely employ this (IHS) classification deviating only where the classification offers appendices or there is a strong clinical rationale. There are many types of headache, and diagnosis is key to proper management. The IHS system is explicit in the sense that it uses features of the headache to make the diagnosis, summing features to make the diagnosis more certain. The general concept is that there are primary and secondary forms of headache. Such a system is outlined in Table 11.1.

Broadly, primary headaches are those in which the headache and its associated features are the disorder in themselves, and secondary headaches are those caused exogenously, such as headache associated with fever. Mild secondary headache, such as that seen in association with upper respiratory tract infections, is common but only rarely worrisome. The clinical dilemma remains that while life-threatening headache is relatively uncommon in western society, suitable vigilance is required by doctors. Primary headache in contrast confers considerable disability over time and, while not life-threatening, certainly robs patients of quality of life.

Secondary headache

It is imperative to establish in the patient presenting with any form of head pain whether there is an important underlying acute cause. Perhaps the most crucial clinical feature to elicit is the length of the history. Patients with a short history require prompt attention and may require quick investigation and management. Patients with a longer history generally require time and patience rather than alacrity. There are some important general features, including associated fever or sudden onset of pain (Table 11.2); these demand attention. Patients with a history of recent onset headache or neurological signs usually need urgent investigation with CT or MRI. Patients with a history of recurrent headache over a period of 1 year or more, fulfilling IHS criteria for migraine (Table 11.3) and with a normal physical examination, have abnormalities demonstrated on brain imaging in only about 1 in 1000 images. In general it should be noted that brain tumour is a rare cause of headache, and an even rarer cause of severe pain.

The management of secondary headache is generally focused on the treatment of the underlying condition, such as an infection or mass lesion. An exception is the condition known as chronic 'post-event' headache in which pain persists for long periods after a trigger. This is an interesting phenomenon that may be seen after CNS infection, trauma, both blunt and surgical, intracranial bleeds, pituitary tumours and other precipitants. While the syndrome is generally self-limiting up to 3–5 years after the event, treatment of the headache may be required if it is disabling. The general principle from the IHS system is that the headache should start within 7 days of the index event. From a clinical viewpoint timing is not so restricted, although from a medicolegal standpoint the rule seems useful. Management is discussed

Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

Table 11.1 Common causes of headache. (After Olesen *et al.* 2005.)

Type	Prevalence (%)
Primary headache	
Migraine	16
Tension-type	69
Cluster headache	0.1
Idiopathic stabbing	2
Exertional	1
Secondary headache	
Systemic infection	63
Head injury	4
Subarachnoid haemorrhage	<1
Vascular disorders	1
Brain tumour	0.1

Table 11.2 Warning signs of serious conditions in patients with head pain.

Sudden onset pain
Fever
Marked change in pain character or timing
Neck stiffness
Pain associated with higher centre complaints
Pain associated with neurological disturbance, such as clumsiness or weakness
Pain associated with local tenderness, such as of the temporal artery

Table 11.3 Simplified diagnostic criteria for migraine. Repeated attacks of headache lasting 4–72 hours that have these features, normal physical examination and no other reasonable cause for the headache. (Adapted from the International Headache Society Classification. Headache Classification Committee of The International Headache Society, 2004.)

At least 2 of	At least 1 of
Unilateral pain	Nausea/vomiting
Throbbing pain	Photophobia and phonophobia
Aggravation by movement	
Moderate or severe intensity	

in the general context of frequent or chronic daily headache below.

Primary headache syndromes

The primary headaches are a group of fascinating disorders in which headache and associated features are seen in the absence of any exogenous cause. The common syndromes (Table 11.1) are tension-type headache, migraine and cluster headache. Some other less well-known syndromes are mentioned because they are easily treated when diagnosed.

Anatomy and physiology of headache

The disabling primary headaches, migraine and cluster headache, have been studied extensively in recent times and are now relatively well understood. In experimental animals the detailed anatomy of the connections of the pain-producing intracranial extracerebral vessels and the dura mater are now defined, building on the classic human observations of Wolff and others. These structures, but not the brain itself, are largely responsible for generating pain from within the head.

The key structures involved in the nociceptive process are:

- The large intracranial vessels and dura mater;
- The peripheral terminals of the trigeminal nerve that innervate these structures;
- The central terminals and second order neurones of the caudal trigeminal nucleus and dorsal horns of C1 and C2: the trigemino-cervical complex.

The innervation of the large intracranial vessels and dura mater by the trigeminal nerve is known as the trigemino-vascular system. The cranial parasympathetic autonomic innervation provides the basis for symptoms, such as lacrimation and nasal stuffiness, which are prominent in cluster headache and paroxysmal hemicrania, although they may also be seen in migraine. It is clear from human functional imaging studies that vascular changes in migraine and cluster headache are driven by these neural vasodilator systems so that these headaches should be regarded as neurovascular. The term vascular headache has no place in modern neurological practice when referring to primary headache.

Migraine is an episodic syndrome of headache with sensory sensitivity, such as to light, sound and head movement, probably caused by dysfunction of aminergic brainstem/diencephalic sensory control systems (Figure 11.1). The first of the migraine, or at least aura, genes have been identified by studying families with familial hemiplegic migraine (FHM), and each involves ion channel dysfunction. Mutations involving the CACNA1A gene encoding the $Ca_v2.1$ P/Q voltage-dependent calcium channel are known to cause FHM-I; this mutation is responsible for about 50% of identified families. Mutations in the *ATP1A2* gene have been identified to be responsible for about 20% of FHM families, and is designated FHM-II. Mutations encoding the neuronal voltage gated sodium channel SCN1A have been identified as the cause of FHM-III, thus continuing the ionopathic theme. Functional neuroimaging has suggested that brainstem regions are involved in the pathogenesis of migraine (Plate 11.1), and a region near the posterior hypothalamic grey matter, the site of the human circadian pacemaker cells of the suprachiasmatic nucleus, in the pathogenesis of cluster headache (Plate 11.2).

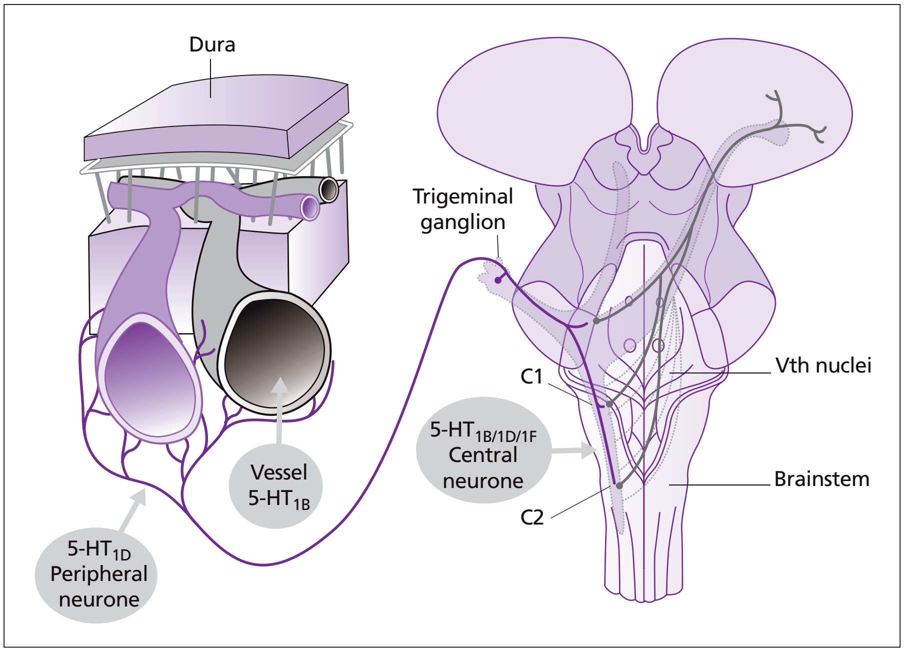


Figure 11.1 Pathophysiology of migraine. Migraine involves dysfunction of brainstem pathways that normally modulate sensory input. The key pathways for the pain are the trigemino-vascular input from the meningeal vessels, which passes through the trigeminal ganglion and synapses on second order neurones in the trigemino-cervical complex. These neurones in turn project in the quinto-thalamic tract, and after decussating in the brainstem, synapse on neurones in the thalamus. Important modulation of the trigemino-vascular nociceptive input, as suggested from brain imaging studies, comes from the dorsal raphe nucleus, locus caeruleus and nucleus raphe magnus.

Migraine

Diagnosis and clinical features

Migraine is generally an episodic headache often with sensitivity to light, sound or movement, and with nausea or vomiting accompanying the headache (Table 11.3). None of the features is an obligatory diagnostic feature. Indeed, a migraine aura, e.g. visual disturbances with flashing lights or zig-zag lines moving across the fields or other neurological symptoms, is reported in only about 20–25% of patients. Most of these patients have visual aura with a small proportion reporting tinnitus, sensory change, weakness, ataxia or dysphasia. There is no evidence that the different neurology of aura alters natural history or treatment so that clinically it is reasonable to label all these presentations as migraine with aura. Thus, a high index of suspicion is required to diagnose migraine. A headache diary can often be helpful in making the diagnosis, although this usually is more helpful in assessing disability or recording how often patients use acute attack treatments. In differentiating the two main primary headache syndromes seen in clinical practice, migraine at its most simple level is headache with associated features, and tension-type headache is headache that is featureless. Most patients who attend doctors with disabling headache probably have migrainous biology.

Most patients with migraine are generally headachy, and inherit a tendency to have headache amplified at various times by their interaction with triggers in their environment. The brain of the migraineur seems more sensitive to stimuli and to change; and this is even more notably amplified in females during their menstrual cycle. The patient with migraine does not habituate to sensory stimuli easily. They may have headache when they or their environment alters the patterns of:

- *Sleep* too little or too much;
- *Eating* skipping meals, or alcohol in particular;
- *Stress* excess stress or in the relaxation phase;
- *Physical activity* such as exertion;
- *Weather* stormy or barometric pressure change;
- *Hormonal environment* such as the menstrual cycle;
- *Afferent stimulation* such as bright lights or loud sounds.

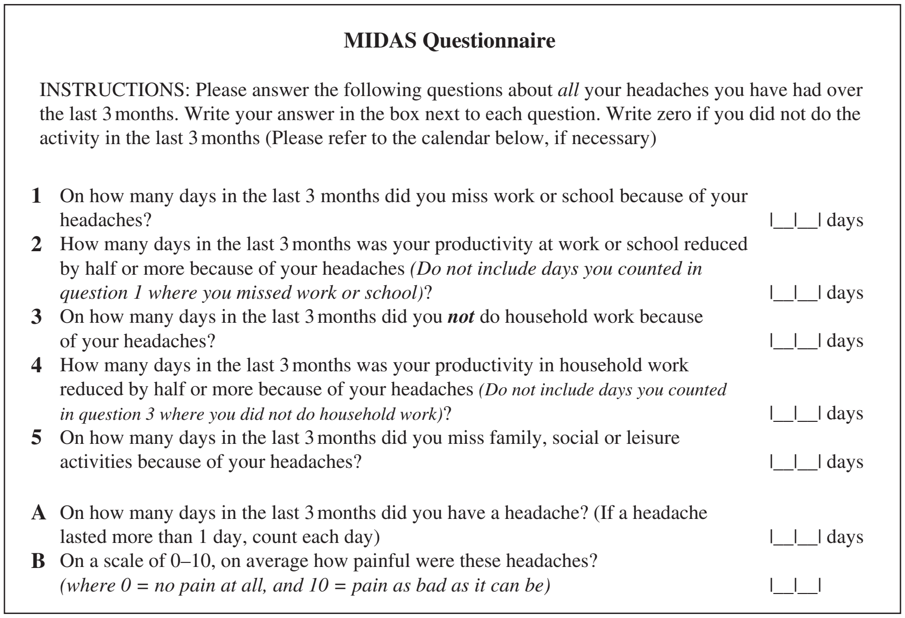
Migraineurs are less tolerant of change and part of successful management is to advise patients to maintain regularity in relation to these critical biological triggers.

It has been said that migraine can never occur daily, but few biological phenomena respect absolute rules. It is now widely accepted that frequent migraine can occur, and this is covered below under chronic daily headache. After making a diagnosis, the second step is to be sure that the disease burden has been fully defined. It is important to ascertain how much headache a patient has, what activities are prevented and what is the degree of disability? Disability can be assessed from the clinical history, a diary or a scale such as the Migraine Disability Assessment Scale (MIDAS), which is well-validated and very easy to use in practice (Figure 11.2). The relationship between vertigo and migraine is discussed in Chapter 14 and retinal migraine in Chapter 13.

Management of migraine

After diagnosis, the management of migraine begins with an explanation of some aspects of the disorder to the patient. It is useful to explain:

- Migraine is an inherited tendency to headache; it is a congenital disorder and therefore it cannot be cured but;



MIDAS Questionnaire

INSTRUCTIONS: Please answer the following questions about *all* your headaches you have had over the last 3 months. Write your answer in the box next to each question. Write zero if you did not do the activity in the last 3 months (Please refer to the calendar below, if necessary)

1 On how many days in the last 3 months did you miss work or school because of your headaches? |__|__| days

2 How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches *(Do not include days you counted in question 1 where you missed work or school)*? |__|__| days

3 On how many days in the last 3 months did you ***not*** do household work because of your headaches? |__|__| days

4 How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches *(Do not include days you counted in question 3 where you did not do household work)*? |__|__| days

5 On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches? |__|__| days

A On how many days in the last 3 months did you have a headache? (If a headache lasted more than 1 day, count each day) |__|__| days

B On a scale of 0–10, on average how painful were these headaches? *(where 0 = no pain at all, and 10 = pain as bad as it can be)* |__|__|

Figure 11.2 MIDAS headache questionnaire. (© Innovative Medical Research 1997.)

- Migraine can be modified and controlled by lifestyle adjustment and the use of medicines;
- Migraine is not life-threatening nor associated with serious illness – except in females who smoke and are on the oestrogenic oral contraceptive pill, where there is a small stroke risk – but migraine can make life a misery;
- Migraine management takes time and sometimes cooperation when, for example, completing a headache diary.

Non-pharmacological management

The main focus of the non-pharmacological management of migraine is the identification and modification of triggering and lifestyle factors. Pamphlets from patient associations can be very helpful to educate sufferers. Those of the American Council for Headache Education (ACHE) and the Migraine Trust and Migraine Action Association in the UK are highly recommended. Nevertheless, many patients will not find such modification of any utility, and it should be explained that the migraine sensitivity of their brains varies. The crucial advice is to explain to the patient that migraine is a state of brain sensitivity to change. This implies that the migraine patient needs to regulate their lives: healthy diet, regular exercise, regular sleep patterns, avoiding excess caffeine and alcohol and, as far as practical, modifying or minimizing stress. The balanced life with less highs and lows will benefit most migraine patients.

Preventive treatments for migraine

The decision to start a patient on a preventive regime is a critical one. It needs to be understood that this is suppressive not curative therapy, and does not alter the underlying diathesis. The patient needs to come to terms with the fact that migraine is an inherited, incurable but manageable problem, and that the medicine is designed to reduce disability. Only then can rational decisions about the choices available be made. The basis of considering preventive treatment from a medical viewpoint is a combination of acute attack frequency and attack tractability. Attacks that are unresponsive to abortive medications are considered for prevention, while simply treated attacks may be less obvious candidates for prevention. The other part of the equation relates to what is happening with time. If a patient diary shows a clear trend of increasing frequency of attacks, it is better to get in early with prevention than wait for the problem to become chronic.

A simple rule for frequency might be that for 1–2 headaches a month there is usually no need to start a preventive, for 3–4 it may be needed but not necessarily, and for 5 or more headaches a month prevention should definitely be on the agenda for discussion. Options available for treatment are covered in detail in Table 11.4 and vary somewhat by country. The problem with preventives is not that there are none, but that they have fallen into migraine from other indications. Often the doses required to reduce headache frequency produce marked and intolerable side effects. This is not surprising if one considers the overall problem of migraineurs to be sensory sensitivity, then one would expect the disorder to contribute to poor tolerability to preventives. It is not clear how preventives work although it seems likely that they modify the brain sensitivity that underlies migraine. Another key clinical point is that generally each drug should be started at a low dose and gradually increased to a reasonable

Table 11.4 Preventive treatments in migraine. Commonly used preventives are listed with reasonable doses and common side effects. The local national formulary should be consulted for detailed information.

Drug	Dose	Selected side effects
β-Blocker		
Propranolol	40–120 mg twice daily	Reduced energy Tiredness Postural symptoms *Contraindicated in asthma*
Tricyclics		
Amitriptyline*		Drowsiness
Dosulepin (dothiepin)	25–75 mg nocte	
Nortriptyline*	**Note*: some patients are very sensitive and may only need a total dose of 10 mg, although generally 1–1.5 mg/kg body weight is required for a response	
Neuromodulators		
Pizotifen	0.5–2 mg/day	Weight gain Drowsiness
Topiramate	25–200 mg/day	Paraesthesia Cognitive symptoms Weight loss Glaucoma Caution with nephrolitiasis
Valproate	400–600 mg twice daily	Drowsiness Weight gain Tremor Hair loss Fetal abnormalities Haematological or liver abnormalities
Gabapentin	900–3600 mg/day	Dizziness Sedation
Methysergide	1–4 mg/day	Drowsiness Leg cramps Hair loss Retroperitoneal fibrosis (1 month drug holiday required every 6 months)
Flunarizine	5–15 mg/day	Drowsiness Weight gain Depression Parkinsonism
No convincing controlled evidence		
Verapamil		
Controlled trials demonstrate no effect		
Nimodipine		
Clonidine		
SSRIs e.g. fluoxetine		

Table 11.5 Oral acute migraine treatments.

Non-specific treatments*	Specific treatments
Aspirin (900 mg)	*Ergot derivatives*
Paracetamol (1000 mg)	Ergotamine (1–2 mg)
NSAIDs	*Triptans*
Naproxen (500–1000 mg)	Sumatriptan (50 or 100 mg)
Ibuprofen (400–800 mg)	Naratriptan (2.5 mg)
Tolfenamic acid (200 mg)	Rizatriptan (10 mg)
	Zolmitriptan (2.5 or 5 mg)
	Eletriptan (40 or 80 mg)
	Almotriptan (12.5 mg)
	Frovatriptan (2.5 mg)

* Often used with antiemetic/prokinetics, such as domperidone (10 mg), prochlorperazine (10–20 mg) or metaclopramide (10 mg).

Table 11.6 Clinical stratification of acute specific migraine treatments.

Clinical situation	Treatment options
Failed analgesics/NSAIDs	*First tier* Sumatriptan 50 or 100 mg p.o. Almotriptan 12.5 mg p.o. Rizatriptan 10 mg p.o. Eletriptan 40 mg p.o. Zolmitriptan 2.5 mg p.o. *Slower effect/better tolerability* Naratriptan 2.5 mg p.o. Frovatriptan 2.5 mg p.o. *Infrequent headache* Ergotamine 1–2 mg p.o. Dihydroergotamine nasal spray 2 mg
Early nausea or difficulties taking tablets	Zolmitriptan 5 mg nasal spray Sumatriptan 20 mg nasal spray Rizatriptan 10 mg MLT wafer
Headache recurrence	Ergotamine 2 mg (most effective p.r./usually with caffeine) Naratriptan 2.5 mg p.o. Almotriptan 12.5 mg p.o. Eletriptan 40 mg
Tolerating acute treatments poorly	Naratriptan 2.5 mg Almotriptan 12.5 mg
Early vomiting	Zolmitriptan 5 mg nasal spray Sumatriptan 25 mg p.r. Sumatriptan 6 mg s.c.
Menstrually related headache	*Prevention* Ergotamine p.o. nocte Oestrogen patches *Treatment* Triptans Dihydroergotamine nasal spray
Very rapidly developing symptoms	Zolmitriptan 5 mg nasal spray Sumatriptan 6 mg s.c. Dihydroergotamine 1 mg i.m.i.

maximum to achieve a clinical effect. The treatment of intractable migraine is discussed below.

Acute attack therapies for migraine

Acute attack treatments for migraine can be usefully divided into disease non-specific treatments (analgesics and non-steroidal anti-inflammatory drugs [NSAIDs]) and disease-specific treatments (ergot-related compounds and triptans; Table 11.5). It must be said at the outset that most acute attack medications seem to have a propensity to aggravate headache frequency and induce a state of refractory daily or near-daily headache – medication overuse headache. It has been argued that this clinical presentation is not a separate headache entity but migrainous phenomenon – an interaction between the patient's biology and particular medicines. Codeine-containing compound analgesics are a particular problem in this regard when available in over-the-counter (OTC) preparations. One should advise patients with migraine who have two headache days a week or more to avoid their regular use. About one-third of patients who stop taking regular analgesics will have substantial improvement in their headache with a reduction in frequency. The other two-thirds will have little or no change to their headache frequency, but will still feel in some way better, especially if they have been using codeine regularly. It is crucial to emphasize to the patient that standard preventive medications generally are ineffective in the face of regular acute attack treatment consumption. It is generally a waste of time to start a preventive in migraine patients if they are using regular analgesics; the analgesic problem should usually be tackled first.

Treatment strategies

Given the array of options to control an acute attack of migraine, how does one start? The simplest approach to treatment has been described as stepped care. In this model all patients are treated, assuming no contraindications, with the simplest treatment, such as 900 mg aspirin or 1000 mg paracetamol (acetaminophen) with an antiemetic. Aspirin is an effective strategy, has been proven so in double-blind controlled clinical trials, and is best used in its most soluble formulations. The alternative would be a strategy known as stratified care, by which the physician determines, or stratifies, treatment at the start based on likelihood of response to levels of care. An intermediate option may be described as stratified care by attack. The latter is what many headache authorities suggest and what patients often do when they have options. Patients use simpler options for their less severe attacks, relying on more potent options when their attacks or circumstances demand them.

Non-specific acute migraine attack treatments

Because simple therapy, such as aspirin and paracetamol (acetaminophen), are cheap and can be very effective, they can be employed in many patients. Dosage should be adequate and the addition of domperidone (10 mg p.o.), prochlorperazine (10–20 mg p.o) metoclopramide (10 mg p.o.) or a serotonin 5-HT_3 receptor antagonist for very severe nausea/vomiting can be very helpful. NSAIDs can be very useful when tolerated. Their success is often limited by inappropriate dosing, and adequate doses of naproxen (500–1000 mg p.o. or p.r. with an antiemetic), ibuprofen (400–800 mg p.o.) or tolfenamic acid (200 mg p.o.) can be extremely effective.

Specific acute migraine attack treatments

When simple measures fail or more aggressive treatment is needed, specific treatments are required. While ergotamine remains useful for some, it can no longer be considered the treatment of choice in acute migraine. There are particular situations in which ergotamine is very useful, but its use must be strictly controlled as overuse can produce dreadful headache and a range of vascular problems. Treatment with a triptan (Table 11.6) has revolutionized the life of many patients and is clearly the most powerful option available to stop a migraine attack. This drug class can be rationally applied by considering the pharmacological features and formulations available. Calcitonin gene-related peptide receptor antagonists are promising additional drugs for the future.

Tension-type headache

Tension-type headache (TTH) is a form of headache which is ill-understood. Although neurologists diagnose TTH commonly, much of the disabling headache that is subsumed in this category is likely to be chronic migraine in terms of its biology (see chronic daily headache). TTH is classified into two forms: episodic TTH, where attacks occur on less than 15 days a month, and chronic TTH where attacks, on average over time, are seen on 15 days or more a month. The latter is part of the broader clinical syndrome of chronic daily headache, but these terms are not synonymous.

Clinical features

TTH has been defined by the IHS, both for its episodic and chronic forms, and includes the additional symptoms of nausea, photophobia or phonophobia in various combinations depending on chronicity. This is without clear biological rationale, and contributes to a level of confusion that has, in this author's view, paralysed useful research on the entity. A useful clinical approach is to diagnose TTH when the headache is completely featureless: no nausea, no vomiting, no photophobia, no phonophobia, no osmophobia, no throbbing and no aggravation with movement. Using such an approach, migraine which has one or more of these features, is the main differential diagnosis of TTH. For research purposes, it is useful to consider separately those patients with attacks of a TTH phenotype who have migraine at other times, a family history of migraine or migrainous illnesses of childhood.

Pathophysiology

The pathophysiology of TTH is very incompletely understood. There is no clear evidence that the headache is, as its name implies, a product of nervous tension, and the definitions currently employed have undoubtedly resulted in the inclusion of patients with migraine into studies. Moreover, the concept that TTH in some way involves muscle contraction is spurious, and evidence shows that muscle contraction is no more likely than in migraine. It seems likely that TTH is a primary disorder of CNS pain modulation alone, to contrast it with migraine, which involves a more generalized disturbance of sensory modulation. There are data suggesting a genetic contribution to TTH, but these data are questionable given the faulty diagnostic criteria.

Management

Adopting the clinical approach, TTH is a headache form that is usually less disabling than migraine. Its episodic form is generally amenable to simple analgesics, paracetamol, aspirin or NSAIDs, which can be purchased OTC. There are clear clinical studies to demonstrate that triptans in TTH alone are not helpful, although triptans are effective in TTH where the patient also has migraine. For chronic TTH, amitriptyline is the only treatment in which evidence shows a clear effect; the other tricylics, selective serotonin re-uptake inhibitors or the benzodiazepines have not been shown in controlled trials to be effective. There is no controlled evidence supporting the use of acupuncture, while there is excellent controlled evidence for behavioural approaches. Placebo controlled trials have been negative when studying the effect of botulinum toxin type A in chronic TTH.

Trigeminal-autonomic cephalalgias I – cluster headache

Cluster headache is a rare form of primary headache, with a population frequency of some 0.1%. It is about as common as multiple sclerosis in the UK, and is a disorder best managed by a neurologist. It is perhaps the most painful human condition and in the cohort of nearly 1000 patients that the author has treated at the National Hospital not a single patient has reported a more painful experience, although some had experience of childbirth, multiple limb fractures and renal stones. Cluster headache is one form of trigeminal-autonomic cephalalgia (TAC) (Table 11.7).

The core feature of cluster headache is periodicity, either circadian or in terms of active and inactive bouts over weeks and months. There is a 3 : 1 male predominance. Typically, one to two episodes of relatively short-duration unilateral pain occur every day in bouts of 8–10 weeks a year. The typical patient is generally perfectly well between bouts. Patients with cluster headache tend to move about during attacks, pacing, rocking or even rubbing their head for relief. The pain is usually retro-orbital boring and very severe. It is associated with ipsilateral symptoms of cranial (parasympathetic) autonomic activation: a red or watering eye,

Table 11.7 Clinical features of the trigeminal autonomic cephalalgias.

	Cluster headache	Paroxysmal hemicrania	SUNCT
Sex	M > F	F = M	F ~ M
Pain			
Type	Stabbing, boring	Throbbing, boring, stabbing	Burning, stabbing, sharp
Severity	Excruciating	Excruciating	Severe to excruciating
Site	Orbit, temple	Orbit, temple	Periorbital
Attack frequency	1/alternate day –8/day	1–40/day (>5/day for more than half the time)	3–200/day
Duration of attack	15–180 min	2–30 min	5–240 s
Autonomic features	Yes	Yes	Yes (prominent conjunctival injection and lacrimation)*
Migrainous features†	Yes	Yes	Yes, about one-third
Alcohol trigger	Yes	No	No
Cutaneous triggers	No	No	Yes
Indometacin effect	–	++	–
Abortive treatment	Sumatriptan injection or nasal spray Oxygen	Nil	Lidocaine (iv)
Prophylactic treatment	Verapamil Methysergide Lithium, steroids	Indometacin	Lamotrigine Topiramate Gabapentin

SUNCT, short-lasting unilateral neuralgiform headache with conjunctival injection and tearing.

* If conjunctival injection and tearing note present consider SUNA (short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms).

† Nausea, photophobia or phonophobia, with typically unilateral photophobia and phonophobia on side of the pain.

++ Indicates absolute response to indometacin.

the nose running or blocking or cranial sympathetic dysfunction (eyelid droop). When present, photophobia or phonophobia is far more likely to be unilateral, on the same side as the pain, than bilateral as is common in migraine. This phenomenon of unilateral photophobia/phonophobia is a generic feature of TACs. Cluster headache is likely to be a disorder involving central pacemaker regions of the posterior hypothalamus or neurones close to it (Plate 11.1).

The TACs – cluster headache, paroxysmal hemicrania and SUNCT – are a distinct group that should be differentiated from short-lasting headaches that do not have prominent cranial autonomic syndromes, notably trigeminal neuralgia, primary stabbing headache and hypnic headache. Differentiation in most patients is possible by determining the cycling pattern, length of attack, frequency and timing of the attacks. The importance of defining this group is threefold. First, the clinical phenotype determines the likely secondary causes that must be considered and appropriate investigations ordered. There is an excess of TAC presentations in patients with pituitary tumour-related headache, and we thus recommend pituitary imaging and pituitary function tests in the evaluation of patients with TACs. Second, diagnosis and classification are important for prognosis and counselling. Third, the correct diagnosis determines therapy.

Management

Cluster headache is managed using acute attack treatments and preventive agents. Acute attack treatments are usually required by all cluster headache patients at some time, while preventives are needed in patients with chronic cluster headache and also shorten the active periods in patients with the episodic form of the disorder.

Preventive treatments

The options for preventive treatment in cluster headache depend on the bout length (Table 11.8). Patients with short bouts require medication that is quick acting but will not necessarily be taken for long periods. Those with long bouts (and those with chronic cluster headache) require safe effective medicines that can be taken often for long periods. Most now favour verapamil as the first-line preventive treatment when the bout is prolonged, or in chronic cluster headache. Limited courses of oral corticosteroids or methysergide can be very useful strategies when the bout is relatively short.

Verapamil compares favourably with lithium in practice, but at doses far in excess of those used in cardiology. Our starting dose is often 40–80 mg twice daily and maintenance doses of up to 960 mg/day. Side effects include constipation and leg swelling, and cardiovascular disturbances. Verapamil can cause heart block

Table 11.8 Preventive management of cluster headache.

Short-term prevention	Long-term prevention
Episodic cluster headache	Episodic cluster headache and prolonged chronic cluster headache
Prednisolone	Verapamil
Methysergide	Lithium
Verapamil	Methysergide
Greater occipital nerve injection	?Topiramate
	?Gabapentin
	?Melatonin

? Unproven but promising.

by slowing conduction in the atrioventricular node as demonstrated by prolongation of the A-H interval. As the PR interval on the electrocardiogram (ECG) is made up of atrial conduction, A-H and His bundle conduction, subtle early effects can be difficult to detect. In our large cohort of patients, about 20% have ECG abnormalities of rhythm on verapamil which begin to occur at doses as low as 240 mg/day, and can also evolve over time in patients on stable doses. Currently, the authors take a baseline ECG and then repeat the ECG 10 days after a dose change, usually 80-mg increments. When verapamil doses exceed 240 mg/day, we advise 6-monthly ECGs for patients on long-term therapy.

Neurostimulation therapy

When medical therapies fail in chronic cluster headache, neurostimulation therapy strategies are now being employed. Deep brain stimulation in the region of the posterior hypothalamic grey matter has been successful in a substantial proportion of patients. We have also similarly good experience with the much less invasive approach of occipital nerve stimulation.

Acute attack treatment

Cluster headache attacks often peak rapidly and thus require a treatment with quick onset. Many patients with acute cluster headache respond very well to treatment with oxygen inhalation. This should be given as 100% oxygen at 10–12 L/min for 15–20 minutes. It is important to have a high flow and high oxygen content. Injectable sumatriptan 6 mg has been a boon for many patients with cluster headache. It is effective, rapid in onset and with no evidence of tachyphylaxis. Sumatriptan 20 mg and zolmitriptan 5 mg nasal sprays are effective in acute cluster headache as established by placebo controlled trials, and offer a useful option for patients who may not wish to self-inject daily. Sumatriptan is not effective when given pre-emptively as 100 mg orally three times daily, and there is no evidence that it is useful when used orally in the acute treatment of cluster headache.

Trigeminal-autonomic cephalalgias II – paroxysmal hemicrania

Sjaastad first reported eight cases of a frequent unilateral severe but short-lasting headache without remission coining the term chronic paroxysmal hemicrania (CPH). The mean daily frequency of attacks varied from 7 to 22 with the pain persisting 5–45 minutes on each occasion. The site and associated autonomic phenomena were similar to cluster headache, but the attacks of CPH were suppressed completely by indometacin. A subsequent review of 84 cases showed a history of remission in 35 cases whereas 49 were chronic. By analogy with cluster headache, the patients with remission have been referred to as having episodic paroxysmal hemicrania and those with the non-remitting form chronic paroxysmal hemicrania; the overall syndrome can be simply called paroxysmal hemicrania. In contrast to cluster headache, which predominantly affects males, the male : female ratio in paroxysmal hemicrania is close to 1 : 1.

In the author's experience, the essential features of paroxysmal hemicrania (PH) are:

- Unilateral very severe pain;
- Short-lasting attacks (2–45 minutes);
- Very frequent attacks (usually more than 5 a day);
- Marked autonomic features ipsilateral to the pain;
- Robust, quick (less than 72 hours), excellent response to indometacin.

Therapy with indometacin can be complicated by gastrointestinal side effects although thus far there is no reliable alternative. We have found topiramate helpful in some cases. Piroxicam is reported to be helpful but is not as effective as indometacin. Verapamil has been used in PH, although the response is not spectacular, but higher doses require exploration. PH can coexist with trigeminal neuralgia, PH-tic syndrome, just as in cluster tic syndrome, and each component requires separate treatment. Secondary PH has been reported with lesions in the region of the sella turcica, an arteriovenous malformation, cavernous sinus meningioma and a parotid epidermoid. Secondary PH is more likely if the patient requires high doses (>200 mg/day) of indometacin and raised cerebrospinal fluid (CSF) pressure should be suspected in apparent bilateral PH. It is worth noting that indometacin reduces CSF pressure by an unknown mechanism. It is appropriate to image patients with MRI when a diagnosis of PH is being considered, particularly to exclude a pituitary lesion.

Trigeminal-autonomic cephalalgias III – SUNCT/SUNA

SUNCT is short-lasting unilateral neuralgiform headache with conjunctival injection and tearing. SUNA is short-lasting unilateral neuralgiform headache with cranial autonomic symptoms.

SUNCT is a rare primary headache syndrome, characterized by unilateral orbital or temporal pain that is stabbing or throbbing in quality and is severe. For diagnostic purposes, there should be a history of at least 20 attacks, lasting for 5–240 seconds with ipsilateral conjunctival injection and lacrimation. In some patients, one or other of the above features are missing, and the diagnosis of SUNA has been suggested.

Diagnosis

A review of 50 cases of SUNCT from the worldwide literature was published in 2003, and there have since been further case reports, as well as a large series of 43 SUNCT and 9 SUNA patients published by the author in 2006. The pain of SUNCT/SUNA is unilateral and may be anywhere in the head. Three basic patterns can be seen: single stabs, which are usually short-lived, groups of stabs or a longer attack comprised of many stabs between which the pain does not resolve to normal, thus giving a 'saw-tooth' phenomenon with attacks lasting many minutes. Important clinical characteristics that lead to the suspicion of a diagnosis of SUNCT are the cutaneous (or other) triggerability of attacks, a lack of refractory period to triggering between attacks and the lack of a response to indometacin. In none of the patients the author has seen was there any response to indometacin compared to saline placebo. Apart from trigeminal sensory disturbance the neurological examination is normal in primary SUNCT.

Secondary (symptomatic) SUNCT

Secondary SUNCT is typically seen with either posterior fossa or pituitary gland lesions. All patients should have brain MRI with pituitary views and pituitary function tests. The diagnosis of SUNCT is often confused with trigeminal neuralgia (Chapter 12), particularly in first division trigeminal neuralgia. Minimal or no cranial autonomic symptoms and a clear refractory period to triggering are useful pointers to a diagnosis of trigeminal neuralgia.

Management of SUNCT/SUNA

Abortive therapy

Because the attacks are so short, attack therapy is not a useful concept in SUNCT/SUNA. One can use short-term prevention in hospital with lidocaine which often arrests the problem.

Preventive therapy

Given the impractical nature of intravenous lidocaine and the short-lasting nature of SUNCT/SUNA attacks, in general terms, preventive therapy is preferred. The most efficacious treatment based on open label studies is with lamotrigine 200–400 mg/day. Other effective treatments include topiramate and gabapentin. Carbamazepine is often reported as helpful by patients but not usually excellent.

Surgical approaches have been used, aimed either at microvascular decompression, which in the author's experience is not useful, or destructive trigeminal procedures, which are seldom useful and often produce long-term complications. Greater occipital nerve injection produces limited effects in some patients, and has had some mixed success with occipital nerve stimulation. One patient has been reported to be completely controlled with deep brain stimulation of the posterior hypothalamic region.

Chronic daily headache

Each of the preceding primary headache forms can occur very frequently. However, when a patient experiences headache on 15 days or more a month, one can apply the broad diagnosis of chronic daily headache (CDH). CDH is collection of very different headache types with different management strategies. Crucially, not all daily headache is simply TTH (Table 11.9). This common clinical misconception confuses the clinical phenotype with the headache biology. Population-based estimates suggest that 4.5–4.8% of Western populations have daily or near daily headache. Daily headache may again be primary or secondary (Table 11.9). Clinical and population-based studies show that many patients with refractory daily headache overuse various OTC preparations. The first step in dealing with patients with CDH is to categorize the correct underlying headache syndrome, for management is essentially that of the underlying condition.

Management

The keys to managing daily headache are:
- Exclude treatable causes (Table 11.9);
- Obtain a clear analgesic history;
- Make a diagnosis of the primary headache type involved.

Management of medication overuse

Out-patients

It is essential to reduce or eliminate analgesic use. Regimes vary from reductions of 10% every week or two, depending on their circumstances or, where there is no contraindication, immediate cessation. A careful diary over a month or two is very helpful in determining the extent of the problem. A small dose of an NSAID, such as naproxen 500 mg twice daily if tolerated, will take the edge off the pain as the analgesic use is reduced. NSAID overuse seems not to be a common problem when given once or twice daily. When the patient has reduced their analgesic use substantially, a preventive should be introduced. It must be emphasized that preventives usually do not work in the presence of analgesic overuse. The most common cause of intractability to treatment is the use of a preventive when analgesics continue to be taken regularly.

In-patients

Some patients will require admission for detoxification. These are broadly two groups: those who fail out-patient withdrawal or who have a significant complicating medical indication, such as brittle diabetes mellitus. When such patients are admitted, acute medications are withdrawn completely on the first day, unless

Table 11.9 Classification of chronic daily headache.

Primary		Secondary
>4 hour/day	<4 hour/day	*Post-traumatic*
Chronic migraine*	Chronic cluster headache[†]	Head injury Iatrogenic (surgery)
		Post-infectious
Chronic tension-type headache*	Chronic paroxysmal hemicrania	*Inflammatory* Giant cell arteritis Sarcoidosis Behçet's syndrome
Hemicrania continua*	SUNCT	Chronic CNS infection
New daily persistent headache*	Hypnic headache	Medication overuse headache

SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

* May be complicated by analgesic overuse. Clinical experience suggests that many patients continue to have headache even after cessation of analgesic use. The residual headache probably represents the underlying headache biology. Whether there is a unique biological basis for medication overuse headache is unclear.

[†] Chronic cluster headache patients may have more than 4 hour/day of headache. The inclusion of the syndrome here is to emphasize that, by and large, the attacks themselves are less than 4 hours' duration.

there is a contraindication. Antiemetics, such as domperidone orally or by suppository, and fluids are administered as required, as well as clonidine for opiate withdrawal symptoms. For acute intolerable pain during the waking hours, aspirin (1 g intravenously) is useful and at night chlorpromazine by injection, after ensuring adequate hydration, can be very helpful. If the patient does not settle over 3–5 days a course of intravenous dihydroergotamine (DHE) can be employed. DHE is administered 8-hourly for 3 days, and can induce a significant remission allowing a preventive treatment to be established. Often 5-HT$_3$ antagonists, such as ondansetron or granisetron, will be required with DHE to prevent nausea.

Preventive treatments

Tricylics, amitriptyline or dosulepin (dothiepin), at doses up to 1 mg/kg are very useful in patients with CDH. Tricyclics are started in low dose (10–25 mg/day) and best given 12 hours prior to waking up to avoid excess morning sleepiness. Other very useful medications are the anticonvulsants, such as topiramate, valproate and gabapentin. For some patients flunarizine can be very effective, as can methysergide or phenelzine.

Treatment of medically intractable disabling chronic daily headache

The management of medically intractable headaches is a common problem in specialist practice. For disabling and completely intractable headache, occipital nerve stimulation is a promising approach, as this seems to modulate thalamic processing in migraine. Previous trials using botulinum toxin in chronic migraine have failed to show objective benefit, although new studies suggest some promise.

Table 11.10 Differential diagnosis of new daily persistent headache.

Primary	Secondary
Migrainous-type Featureless (tension-type)	Subarachnoid hemorrhage Low CSF volume headache Raised CSF pressure headache Post-traumatic headache* Chronic meningitis

CSF, cerebrospinal fluid.

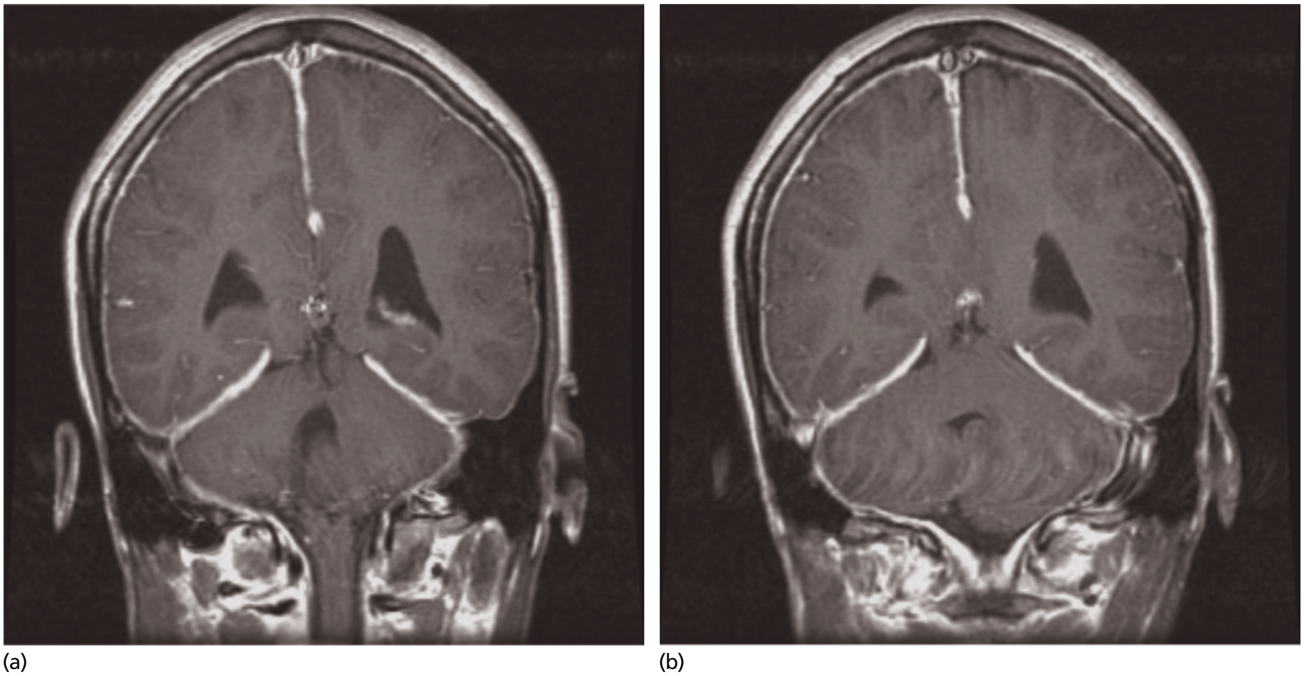
* Includes post-infective forms.

New daily persistent headache

New daily persistent headache (NDPH) is a clinically distinct syndrome with a range of important possible causes (Table 11.10). Nosologically, the IHS has chosen a narrow definition of this syndrome that this author does not find clinically useful. Using a clinically orientated approach NDPH can have both primary and secondary forms (Table 11.10) and neurologists will be called on to diagnose and treat these patients.

Clinical presentation

The patient with NDPH presents with a history of headache on most if not all days. The onset of headache is abrupt and the headache persistent. In a classic case, if that term is appropriate, the patient will recall the exact day and circumstances that the headache developed and then never resolved. Diagnostically, it is first important to exclude secondary forms of headache. Subarachnoid



(a) (b)

Figure 11.3 Magnetic resonance image showing diffuse meningeal enhancement after gadolinium administration in a patient with low cerebrospinal fluid (CSF) volume (pressure) headache.

haemorrhage can certainly develop acutely, but is not likely to cause diagnostic confusion in this group of patients.

Low CSF volume headache

The syndrome of persistent low CSF volume headache is an important diagnosis not to miss. The most immediate precipitant in neurological practice is lumbar puncture. In that setting the headache settles rapidly with bed rest. In the chronic situation the patient typically presents with a history of headache every day. The pain is generally not present on waking, worsens during the day and is relieved by lying down. Recumbency usually improves the headache in minutes, and it takes only minutes to an hour for the pain to return when the patient is upright again. The patient may give a history of an index event: lumbar puncture or epidural injection, or a vigorous Valsalva, such as with lifting, straining, coughing, clearing the Eustachian tubes in an aeroplane or multiple orgasm. Patients may volunteer, or a history may be obtained, that beverages with caffeine provide temporary respite. Spontaneous leaks are well recognized, and the clinician should not be put off the diagnosis if the headache history is typical when there is no obvious index event. As time passes from the index event, the postural nature may be less obvious; certainly cases whose index event was several years prior to the eventual diagnosis are recognized. The term low volume rather than low pressure is used, because there is no clear evidence at which point the pressure can be called low. While low pressures, such as 0–5 are usually identified, a pressure of 16 cm CSF has been recorded with a documented leak.

The investigation of choice is MRI with gadolinium (Figure 11.3), which produces a striking pattern of diffuse pachymeningeal enhancement; although in about 10% of cases a leak can be documented without enhancement. The finding of diffuse meningeal enhancement is so typical that, depending on clinical context, immediate treatment is appropriate. It is also common to see Arnold–Chiari malformations on MRI with some degree of descent of the cerebellar tonsils. This is important from the neurologist's viewpoint because surgery in such settings simply makes the headache problem worse. Alternatively, the CSF pressure may be determined, or a leak sought with ^{111}In-DTPA. CSF studies that can demonstrate the leak directly, or be suggestive, such as the finding of early emptying of tracer into the bladder or slow progress of tracer across the brain.

Treatment is bed rest in the first instance. False positive transient improvement in persistent low CSF volume headache with chiropractic and other similar therapies is recognized where the treatment necessitated the patient lying down for a prolonged period. Intravenous caffeine (500 mg in 500 mL saline administered over 2 hours) is often very efficacious. The ECG should be checked for any arrhythmia prior to administration. A reasonable practice is to carry out at least two infusions separated by 4 weeks after obtaining the suggestive clinical history and MRI with enhancement before any more elaborate tests. Because intravenous caffeine is safe and can be curative, by an unknown mechanism, it spares many patients the need for further investigations. If that is unsuccessful, an abdominal binder may be helpful. If a leak can be identified, either by the radioisotope study, by CT myelogram or spinal T2-weighted MRI, an autologous blood patch is usually curative. In more intractable situations theophylline is a useful alternative although its effect is rather slow in the author's experience.

Raised CSF pressure headache

Raised CSF pressure as a cause of headache is well recognized by neurologists. Brain imaging often reveals the cause. Idiopathic intracranial hypertension can be a diagnostic problem where patients present with headache without visual problems and with normal fundi. It is recognized that intractable chronic migraine can be triggered by persistently raised intracranial pressure. These patients typically give a history of generalized headache that is present on waking, and gets better as the day goes on. It is generally worse with recumbency. Visual obscurations are frequently reported. Fundal changes on raised intracranial pressure would make the diagnosis relatively straightforward but it is in those without such changes that the history must drive investigation. Two important differential diagnoses are the headaches, usually occurring in the morning, caused by obstructive sleep apnoea causing morning headache, or poorly controlled hypertension.

If raised pressure is suspected, brain imaging is mandatory. The CSF pressure should be measured by lumbar puncture taking care to do so when the patient is symptomatic, so that both the pressure and response to removal of 20–30 mL CSF can be determined. A raised pressure and improvement in headache with removal of CSF is diagnostic. The fields should be formally documented even in the absence of overt ophthalmic involvement. Initial treatment can be with acetazolamide (250–500 mg twice daily). Improvement of headache can occur within weeks. If this is not effective topiramate may be useful in this setting. A small number of severely disabled patients who do not respond to medical treatment will come to intracranial pressure monitoring and occasionally require a ventricular shunt.

Post-traumatic headache

The issue of post-traumatic headache is a vexed one. The IHS accepts the existence of such a syndrome although it remains ill-defined. The term is used here to include NDPH after a blow to the head or infective episode, typically presumed viral meningitis, although it can occur after parasitic infection. In a recent series, one-third of patients with NDPH reported the headache starting after a flu-like illness. The headache starts during that period and never remits. Investigation reveals no obvious cause. It has been suggested that some patients with this syndrome have a persistent Epstein–Barr infection, but this syndrome has not been clearly delineated. A complicating factor is that lumbar puncture may have been carried out during that illness, so a persistent low CSF volume headache needs to be considered. Post-traumatic headache may be seen after carotid dissection, subarachnoid haemorrhage and following intracranial surgery for a benign mass.

The treatment of this form of NDPH is essentially empirical. Tricyclics, notably amitriptyline, and anticonvulsants, topiramate, valproate and gabapentin, have been used with good effects. The monoamine oxidase inhibitor (MAOI) phenelzine can also be useful in carefully selected patients. On the positive side, the headache runs a limited course of 3–5 years and will eventually settle. It can certainly be very disabling.

Primary new daily persistent headache

Initial descriptions of primary NDPH found an equal incidence in males and females. Migrainous features were common, with unilateral headache in about one-third and throbbing pain in about one-third. Nausea was reported in about half of patients, as was photophobia and phonophobia. A number of these patients have a previous history of migraine but not more than one might expect given the population prevalence of migraine. In the initial report of this condition, 86% of patients were headache free at 24 months. Primary NDPH can occur with other features or without. Featureless NDPH is perhaps the most refractory form of primary headache that is encountered in clinical practice.

Other primary headaches

Hemicrania continua

Two patients were initially reported with this syndrome, a woman aged 63 years and a man of 53. They developed unilateral headache without obvious cause. One of these patients noticed redness, lacrimation and sensitivity to light in the eye on the affected side. Both patients were relieved completely by indometacin while other NSAIDs were of little or no benefit. Newman and colleagues (1994) reviewed the 24 previously reported cases and added 10 of their own, including some with pronounced autonomic features resembling cluster headache. They divided their case histories into remitting and unremitting forms. Of the 34 patients reviewed, 22 were women and 12 men with the age of onset ranging from 11 to 58 years. The symptoms were controlled by indometacin 75–150 mg/day. The essential features of hemicrania continua:

- Unilateral pain;
- Pain is moderate and continuous but with fluctuations of often severe pain;
- Complete resolution of pain with indometacin;
- Exacerbations may be associated with autonomic features.

Apart from analgesic overuse as an aggravating factor, and a report in an HIV-infected patient, the status of secondary hemicrania continua is unclear. The 'indotest' – the intramuscular injection of indometacin 50 mg – is a diagnostic tool. The approach has been refined with the use of a placebo controlled indometacin test. An alternative is a trial of oral indometacin, initially 25 mg three times daily, then 50 mg three times daily and then 75 mg three times daily, with 2-weekly incremental steps. Emerging evidence suggests that occipital nerve stimulation may have a role in the treatment of patients with hemicrania continua who are intolerant to indometacin.

Primary stabbing headache

Short-lived jabs of pain, defined by the IHS as primary stabbing headache, are well documented in association with most types of primary headache. The essential clinical features:

- Pain confined to the head, although rarely is it facial;
- Stabbing pain lasting from one to many seconds or minutes, and occurring as a single stab or a series of stabs;
- No associated cranial autonomic features;
- No cutaneous triggering of attacks;
- Recurring at irregular intervals (hours to days).

These pains have been variously described as 'ice-pick' pains, or 'jabs and jolts'. They are more common in patients with other primary headaches, such as migraine, the TACs and hemicrania continua. The response of primary stabbing headache to indometacin (25–50 mg twice to three times daily) is generally excellent. As a general rule, the symptoms wax and wane and after a period of control on indometacin it is appropriate to withdraw treatment and observe the outcome. Most patients will not want treatment when the nature of the problem is explained and reassurance given that the attacks are not sinister in any way.

Primary cough headache

Sharp pain in the head on coughing, sneezing, straining, laughing or stooping has long been regarded as a symptom of organic intracranial disease, commonly associated with obstruction of the CSF pathways. The presence of an Arnold–Chiari malformation or any lesion causing obstruction of CSF pathways or displacing cerebral structures must be excluded before cough headache is assumed to be benign. Cerebral aneurysm, carotid stenosis and vertebro-basilar disease may also present with cough or exertional headache as the initial symptom. The term 'benign Valsalva manoeuvre-related headache' covers the headaches provoked by coughing, straining or stooping but cough headache is more succinct and so widely used it is unlikely to be displaced. The essential clinical features of benign cough headache:

- Bilateral headache of sudden onset, lasting minutes, precipitated by coughing;
- May be prevented by avoiding coughing or other precipitating event;
- Diagnosed only after structural lesions, such as posterior fossa tumour, have been excluded by neuroimaging.

Comparing benign cough with benign exertional headache, The average age of their patients with benign cough headache is 43 years older than their patients with exertional headache. Indometacin is the medical treatment of choice in cough headache. Raskin (1995) followed up an observation of Sir Charles Symonds reporting that some patients with cough headache are relieved by lumbar puncture. LP is a simple option when compared to prolonged use of indometacin, and in the author's experience works in about one-third of patients. The mechanism of this response remains unclear.

Primary exertional headache

The relationship of this form of headache to cough headache and also to migraine is unclear. Credit must be given to Hippocrates for first recognizing this syndrome when he wrote: 'One should be able to recognize those who have headache from gymnastic exercises, or walking, or running, or any other unseasonable labour, or from immoderate venery'. The clinical features are:

- Pain specifically brought on by physical exercise;
- Bilateral and throbbing in nature at onset and may develop migrainous features in those patients susceptible to migraine;
- Lasts from 5 minutes to 24 hours;
- Prevented by avoiding excessive exertion, particularly in hot weather or at high altitude (see acute mountain sickness, Chapter 18).

The acute onset of headache with straining and breath-holding as in weightlifter's headache may be explained by acute venous distension. The development of headache after sustained exertion, particularly on a hot day, is more difficult to understand. Anginal pain may be referred to the head, probably by central connections of vagal afferents and may present as exertional headache, so-called cardiac cephalgia. The link to exercise is the main clinical clue. Phaeochromocytoma may occasionally be responsible for exertional headache. Intracranial lesions or stenosis of the carotid arteries may have to be excluded as discussed for benign cough headache. Headache may be precipitated by any form of exercise and often has the pulsatile quality of migraine.

Management

The most obvious advice is to take exercise gradually and progressively whenever possible. Indometacin at daily doses varying from 25 to 150 mg is generally very effective in benign exertional headache. Indometacin 50 mg, ergotamine 1 mg orally, dihydroergotamine by nasal spray or methysergide 1–2 mg orally given 30–45 minutes before exercise are useful prophylactic measures.

Primary sex headache

Sex headache may be precipitated by masturbation or coitus and usually starts as a dull bilateral ache while sexual excitement increases, suddenly becoming intense at orgasm. The term orgasmic cephalgia is not useful because not all types of sex headache require orgasm. Three types of sex headache are discussed: a dull ache in the head and neck that intensifies as sexual excitement increases, a sudden severe ('explosive') headache occurring at orgasm and a postural headache resembling that of low CSF pressure developing after coitus. The latter is in fact another form of low CSF pressure headache arising from vigorous sexual activity usually with multiple orgasms and is more usefully considered with NDPH as a secondary chronic daily headache (Table 11.9).

The essential clinical features of sex headache:

- Precipitation by sexual excitement;
- Bilateral at onset;
- Prevented or eased by ceasing sexual activity before orgasm.

Headaches developing at the time of orgasm are not always benign. Subarachnoid haemorrhage is sometimes precipitated by sexual intercourse. Sex headache affects, or at least is reported, by men more often than women and may occur at any time during the years of sexual activity. It may develop on several occasions in succession and then not trouble the patient again, although there is no obvious change in sexual technique. If sexual activity is ceased when headache develops, the headache may subside within a period of 5 minutes to 2 hours. It is recognized that more frequent orgasm can aggravate established sex headache. About half of patients with sex headache have a history of exertional headaches, but there is no excess of cough headache. In about 50% of patients, sex headache will settle in 6 months. Migraine is probably more common in patients with sex headache.

Management

Benign sex headaches are usually irregular and infrequent in recurrence, so management can often be limited to reassurance and advice about ceasing sexual activity if a milder warning headache develops. When the condition recurs regularly or frequently, it can be prevented by the administration of propranolol, but the dosage required varies from 40 to 200 mg/day. An alternative is the calcium channel blocking agent diltiazem 60 mg three times daily. Ergotamine (1 mg) or indometacin (25–50 mg) taken about 30–45 minutes prior to sexual activity can also be helpful.

Primary thunderclap headache

Sudden onset severe headache may occur in the absence of any precipitant. The differential diagnosis includes the sentinel bleed of an intracranial aneurysm, cervico-cephalic arterial dissection and cerebral venous thrombosis. Headaches of explosive onset may also be caused by the ingestion of sympathomimetic drugs or tyramine-containing foods in a patient who is taking MAOIs, and can also be a symptom of phaeochromocytoma. Whether thunderclap headache can be the presentation of an unruptured cerebral aneurysm is argued.

Wijdicks *et al.* (1998) followed up 71 patients whose CT scans and CSF findings were negative for an average of 3.3 years. Twelve patients had further such headaches, and 31 (44%) later had regular episodes of migraine or tension-type headache. Factors identified as precipitating the headache were sexual intercourse in three cases, coughing in four and exertion in 12, while the remainder had no obvious cause. A history of hypertension was found in 11 and of previous headache in 22. None of the patients developed serious pathology in the long term.

The presentation of 37 patients with subarachnoid haemorrhage has been compared with 189 with a similar thunderclap headache but normal CSF; the authors could not discern any characteristic to distinguish the two conditions on clinical grounds.

Investigation of any sudden severe headache, be it in the context of sexual excitement or isolated thunderclap headache, depends on the context. The first episode should be vigorously investigated with CT and CSF examination, and usually also MRI/MRV/MRA. Formal cerebral angiography should be reserved for cases in which clinical presentation is particularly suggestive of intracranial aneurysm. Reversible segmental cerebral vasoconstriction may be seen in primary thunderclap headache without there being an intracranial aneurysm. Posterior leucoencephalopathy, another cause of sudden headache, occurs in cerebral angiitis, with ciclosporin A, intrathecal methotrexate/cytarabine, pseudoephedrine or cocaine use, post-transfusion and postpartum angiopathy, and in eclampsia.

Hypnic headache

This syndrome was first described in patients aged 67–84 years who had headache of a moderately severe nature that typically came on a few hours after going to sleep. These headaches last 15–30 minutes, are typically generalized, although may be unilateral, and can be throbbing. Patients may report falling back to sleep only to be awoken by a further attack a few hours later with up to three repetitions of this pattern over the night. In the largest series of 19 patients, 16 (84%) were female and the mean age at onset was 61 ± 9 years. Headaches were bilateral in two-thirds and unilateral in one-third and in 80% of cases mild or moderate. Three patients reported similar headaches when falling asleep during the day. None had photophobia or phonophobia and nausea is unusual. Poorly controlled hypertension needs to be excluded, and 24-hour blood pressure monitoring is carried out in all patients in the author's practice.

Management

Patients with hypnic headache generally respond to a bedtime dose of lithium carbonate (200–600 mg) and in those who do not tolerate this, verapamil or methysergide at bedtime may be alternative strategies. Two patients who responded to flunarizine 5 mg at night have now been reported. One to two cups of coffee or caffeine 60 mg orally at bedtime may be helpful. This is a simple approach, effective in about one-third of patients. A patient poorly tolerant of lithium has been controlled using verapamil at night (160 mg).

Acknowledgement

Some parts of this work have appeared previously in Goadsby PJ. Headache. In: Fowler TJ, Scadding JW, eds. *Clinical Neurology*, 3rd edn. London: Edward Arnold Ltd, 2003

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12

Cranial Nerve Disorders

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This chapter reviews typical features of lesions of individual cranial nerves and conditions affecting them, and some combinations of cranial nerve lesions. Conditions affecting the optic nerves and cranial nerves III, IV and VI are discussed in Chapter 13. Neuro-otological conditions are discussed in Chapter 14 and the anatomy of the cranial nerves, their nuclei and central connections in Chapter 2.

I. Olfactory nerve

Complaints about disorders of the sense of smell are relatively common; they are sometimes almost unnoticed by patients and tend to be downplayed by clinicians. Loss of olfaction is often an underestimated disability; it is of great importance in the professions where differentiation of complex odours is vital. Although seldom regarded as a major handicap, anosmia or hyposmia but may be the first manifestation of a serious underlying disorder. Olfaction can be difficult to test in practice and is often not examined routinely.

Functional anatomy

Humans have two nasal chemosensory systems: the olfactory nerve system responsible for detecting odours, and trigeminal afferents that respond to irritants, high concentrations of odorants and the sensation of coolness, e.g. of menthol vapour. Thus, in patients with anosmia resulting from lesions of the olfactory nerve, the response to nasal irritation from ammonia or menthol is still preserved. The olfactory pathways and the subtleties of the complex mechanisms of olfaction are described in Chapter 2.

Symptoms

Anosmia refers to complete loss of sense of smell and partial anosmia to loss of ability to detect certain smells. Hyposmia indicates generally diminished sense of smell. Dysosmia is distorted sense of smell, e.g. when pleasant odours smell unpleasant. Phantosmia refers to a sensation of smell that is constantly present, in the absence of objective odour.

Patients with impaired olfactory function also usually complain of loss of taste. This is because most of the perceived flavour of food is derived from smell rather than taste: try tasting food or drink with the nostrils occluded. The four basic tastes – sweet, sour, salty and bitter – are subserved by Vth, VIIth and IXth nerve afferents. These remain intact in the patient with anosmia. Many people with gradual loss of smell over many years are unaware of the problem. Dysosmia and phantosmia, often with perception of a foul or medicinal odour, may occur during olfactory epithelium degeneration and regeneration; this can occur following an upper respiratory infection or paranasal sinus infection, or following head trauma. These complaints are also noted frequently following cancer chemotherapy and cranial radiotherapy; recovery is usual but not invariable.

It is important to determine the tempo of onset and to distinguish clinically between total bilateral loss of sense of smell and unilateral loss, rarely noticed by patients; the latter can point to a lateralized lesion of the olfactory system. A history of local nasal symptoms indicative of nasal congestion, allergic rhinitis or sinusitis should be sought. A recent upper respiratory tract infection may be relevant. Past history of head injury, exposure to toxic fumes, drugs, chemotherapy or radiotherapy, excessive alcohol, smoking and cocaine use, systemic diseases, and features of Parkinson's disease or cognitive impairment may all provide clues to aetiology. Kallmann's syndrome is a rare cause of anosmia resulting from failure of the olfactory lobes to develop, with secondary hypogonadism caused by gonadotropic hormone deficiency.

Examination

Detailed smell testing is difficult in routine clinical practice. The usual assessment is to ask patients to sniff vials containing odours such as peppermint oil, cloves or coffee, using each nostril in turn with the other occluded. The examiner should be aware that even with a normal sense of smell it may be difficult for many people

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Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

to identify these odours – the crux of the matter is to distinguish them. Non-organic anosmia may be suggested by the loss of ability to detect ammonia, which causes nasal irritation because of stimulation of trigeminal afferents within the nose; such testing with irritants should be carried out with particular care, if at all. However, all tests of this sort are relatively crude. More detailed testing of olfaction is possible using commercially available tests such as the University of Pennsylvania Smell Identification Test (UPSIT), a standardized panel of 40 microencapsulated 'scratch and sniff' odours with multiple choice identification of each. A percentile ranking, compared to age- and gender-matched controls is obtained and olfactory function may be classified into one of six categories from anosmia to normal, and includes malingering. Other shorter quantitative smell testing kits are also commercially available. There are no readily available objective neurophysiological tests, although evoked responses are used in some research protocols.

In addition to testing olfaction, taste should be tested in patients with olfactory disorders, and the mouth, nose and sinuses examined. Endoscopic examination by an ENT specialist is usually necessary.

Causes of anosmia

Olfactory disorders are caused either by transport disorders brought about by local obstruction of the nasal passages or sensori-neural impairment from damage to the olfactory neuroepithelium, olfactory nerve or its central connections.

Ageing

Age-related reduction in sense of smell is the norm. About half of the population between the ages of 65 and 80 years have significant impairment of sense of smell, a figure that rises to almost three-quarters after the age of 80. This diminution of smell with age may contribute to the loss of appetite that sometimes occurs in the elderly. The number of olfactory receptors and neurones decreases with age and there may be cumulative damage from viruses and degenerative change. In some cases bone growth around the ethmoid, leading to compression of the olfactory fila, may be a cause.

Upper respiratory infections, nasal and paranasal sinus disease

Viral upper respiratory tract infections, including the common cold and influenza, are probably the most common cause of permanent loss of smell. Often the infection is more severe than usual and is remembered by the patient. Damage to the olfactory epithelium and receptors, including the basal cells from which receptor cells regenerate, is probably the cause. A wide variety of allergic and infective nasal disorders, including chronic rhinitis and sinusitis, as well as disorders causing nasal obstruction, may all be associated with anosmia.

Trauma and surgery

Acceleration–deceleration of the brain following injury can shear the delicate olfactory fila as they pass through the cribriform plate of the ethmoid, with or without fracture of the cribriform plate itself. A fall on to the occipital region can cause this, without loss of consciousness, sometimes with frontal lobe contracoup injury. Anosmia is also associated with more severe traumatic brain injury with evident damage to the olfactory bulb and frontal cortical and subcortical structures; nasal trauma may also be a contributing factor in some cases. Transient dysosmia can occur soon after injury; recovery of olfactory function occurs in 30–40% but is unlikely if symptoms persist for longer than a year. Anosmia, unilateral or bilateral can follow surgery to the sub-frontal region, sometimes with a persistent CSF leak and risk of meningitis.

Neurodegenerative disorders

Impaired olfactory function has been well described in Parkinson's disease, dementia with Lewy bodies, Alzheimer's disease, Huntington's disease, motor neurone disease, Korsakoff syndrome and multiple sclerosis (MS). In Parkinson's disease, the anterior olfactory structures including the olfactory bulb and anterior olfactory nucleus have been shown to be involved, with Lewy body formation at an early stage of the disease. Similarly, in Alzheimer's disease, profound neuronal loss is seen in the olfactory bulb and limbic brain regions, areas that receive olfactory input become heavily laden with neurofibrillary tangles and plaques. In MS, olfactory loss is in direct proportion to the burden of demyelinating lesions in areas of the brain associated with olfactory processing (frontal and temporal regions).

In idiopathic Parkinson's disease, hyposmia predates the onset of motor symptoms, often by many years or even decades. Impaired olfactory function is found in up to 90% of patients with Parkinson's disease, irrespective of disease duration or severity. Perception of certain odours such as petrol, banana, smoke and cinnamon seem to be lost preferentially on detailed testing. Demonstration of hyposmia may be useful in the differential diagnosis of parkinsonian disorders, because other extrapyramidal disorders such as progressive supranuclear palsy, vascular parkinsonism and cortico-basal degeneration are not associated with an increased prevalence of impaired olfaction than age-matched controls. However, hyposmia is sometimes seen in multiple system atrophy. There has been recent interest in olfactory testing as a biomarker of preclinical Parkinson's and Alzheimer's diseases.

Other causes of olfactory dysfunction

Olfactory groove meningiomas are an important, if rare, cause of unilateral anosmia; impairment of smell may be the only or principal symptom of this treatable disorder. Eventually, unilateral visual loss resulting from posterior extension to involve the optic nerve and dementia because of frontal lobe involvement may follow. Other structural lesions such as pituitary tumours and aneurysms may also compress the olfactory tract below the frontal lobes. Toxic exposure to a wide variety of industrial agents including acids, acetone, solvents and benzene have been anecdotally related to impaired smell, possibly because of direct damage to the olfactory receptor cells in some cases. The highly metabolically active receptor cells are also vulnerable to exposure to a number of drugs including antibiotics, anti-inflammatory agents, antithyroid drugs, antimetabolites and chemotherapeutic agents or radiotherapy – the latter two can irreversibly damage the ability of olfactory receptor cells to proliferate. Similarly, cigarette smoking impairs olfactory ability, usually with recovery after abstinence.

A variety of medical disorders such as cirrhosis, renal failure, hypothyroidism and vitamin deficiency (vitamins A, B_6 and B_{12}) can cause impaired olfaction. Olfactory receptor cells may be congenitally absent in Kallmann's syndrome, Turner's syndrome and albinism.

Damage to cortical structures involved in olfactory processing can lead to impaired odour identification or impairment of recognition memory but rarely to total anosmia. Olfactory hallucinations are well-recognized as part of the aura preceding a temporal lobe seizure; such hallucinations rarely occur as the sole manifestation of a seizure (Chapter 6). An unpleasant but stereotyped smell is usually described but it is rarely an identifiable odour. Olfactory hallucinations may also occur in depression, schizophrenia and alcohol withdrawal. The complaint of a constant foul smell, or of a distortion of smell with everything smelling unpleasant, may sometimes be a result of suppurative paranasal sinus infection, but is more often of psychotic origin or associated with depressive illness.

V. Trigeminal nerve

The trigeminal is the largest cranial nerve. It contains sensory and motor components, the sensory territory including the face and head anterior to the vertex, the mucous membranes of the oral and nasal cavities, paranasal sinuses, the teeth, intracranial vessels and the dura of the anterior and middle cranial fossae. The motor root supplies the muscles of mastication. Detailed anatomy is considered in Chapter 2. The distribution of the three peripheral divisions of the nerve is shown in Figure 12.1 and the arrangement of the distribution of the spinal Vth nucleus in Figure 12.2.

Examination

Motor and sensory functions of the trigeminal nerve need to be examined separately. Sensory examination should include examination of all three divisions of the nerve and comparison made with the other side. Cutaneous sensation including light touch, pin-prick and temperature should all be tested. In practice, temperature sensation is often quickly assessed with a cold metal tuning fork, asking if the patient can appreciate the cool temperature of the metal against the facial skin. Remember that the angle of the jaw is usually outside the trigeminal territory and that V_1, the ophthalmic division includes the side of the nose and extends back to the vertex. The back of the scalp and angle of the jaw are supplied by the C2/3 dermatomes. Non-organic patterns of

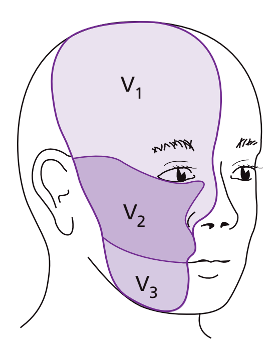

Figure 12.1 Cutaneous distribution of the three divisions of Vth nerve. (From Patten 1996, with permission.) Precise distribution varies amongst published sources.

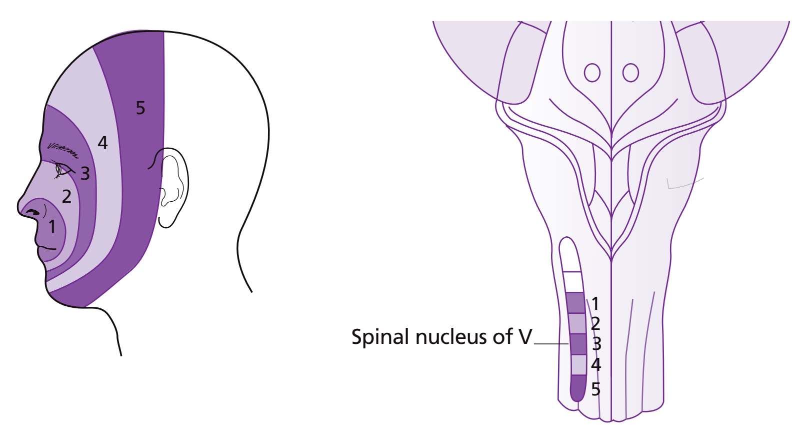

Figure 12.2 Facial distribution of spinal Vth nucleus.

sensory loss may include the angle of the jaw or stop at the hairline. Caution in hasty interpretation of these signs is essential; organic disease may occasionally result in similar patterns of sensory loss, e.g. in syringomyelia.

The corneal reflex (Chapters 2, 3 and 19) is elicited with a wisp of cotton wool or sometimes by wafting air gently over the cornea while shielding the other eye. The afferent arc is mediated by V_1 for the upper cornea and V_2 for the lower portion of the cornea (Chapter 2); the efferent arc is via the facial nerve (blink) and nervus intermedius (lacrimation). In the normal corneal response, there is discomfort when the cornea is touched, accompanied by tearing and conjunctival injection. Abnormalities of the corneal reflex are an early sensitive sign of trigeminal nerve sensory dysfunction; neurophysiological recording of the related blink reflex may be a useful way of quantifying an abnormality.

Tactile sensory loss on the face in the absence of a reduced or absent corneal reflex should raise suspicion of a non-organic cause. Parietal lobe lesions (involving the peri-sylvian portion of the post-central gyrus) can cause depression of contralateral corneal sensation.

The muscles of mastication are tested, first by asking the patient to clench the jaw, palpating the muscles and looking for fasciculation. Strength of jaw opening and lateral deviation against resistance are also examined. Unilateral lesions causing jaw deviation towards the affected side (contralateral pterygoid contraction) and inability to deviate the jaw to the opposite side. The jaw jerk is elicited with the jaw relaxed and slightly open. The afferent arc is via stretch receptors in V_3 and the efferent arc via the trigeminal motor fibres. An absent jaw jerk is rarely helpful. An exaggerated jaw jerk indicates bilateral supranuclear lesions of the corticobulbar pathways rostral to the pons (e.g. pseudobulbar palsy).

Peripheral Vth nerve lesions

Lesions of individual divisions and peripheral branches produce well-demarcated areas of sensory loss on the face and sometimes considerable pain. Trauma is a frequent cause; the supra-orbital and infra-orbital branches of V_1 are among the nerves most commonly affected. Numbness of half of the tongue accompanied by occipital and upper neck pain on head turning is a feature of the neck–tongue syndrome, believed to be caused by compression of the ventral ramus of C2 that carries sensory fibres from the tongue via the hypoglossal nerve. The ophthalmic, maxillary and mandibular divisions may be affected individually or in combination as they exit the skull base (through the superior orbital fissure, foramen rotundum and foramen ovale) by malignant meningeal infiltration, infective or granulomatous meningeal processes, or bony metastases in the skull. The Gasserian ganglion may be affected by similar processes at the petrous tip, causing ipsilateral sensory disturbance in the face; the abducens nerve may also be affected in this area (Gradenigo syndrome). Trigeminal schwannomas may arise from the region of the trigeminal ganglion, either as an isolated tumour or as part of the spectrum of neurofibromatosis Type 2. The trigeminal nerve may be involved in cerebellopontine angle syndromes (see below).

Numb chin syndrome

Unilateral sensory disturbance affecting the chin and lower lip is a distinctive, important syndrome. It usually indicates a bony metastasis in the mandible involving the mental nerve. This can be a feature of a breast or prostate cancer recurrence, lymphoma or myeloma. Some cases are caused by more proximal infiltration of V_3. Non-malignant disorders affecting the mandible can also present in this way. A variant is the numb cheek syndrome – compromise of the infra-orbital nerve in the infra-orbital foramen, or caused by proximal involvement of V_2.

Superior orbital fissure syndrome

The ophthalmic division through the superior orbital fossa (SOF) together with the IIIrd, IVth and VIth cranial nerves (Chapter 13), may be involved in various combinations by pathological processes at this site. The typical presentation is with ophthalmoplegia accompanied by sensory disturbance and often pain in V_1 distribution, sometimes in combination with proptosis with large orbital lesions. Horner's syndrome and visual loss may also occur if the sympathetic supply to the eye or optic nerve become involved, the latter suggesting extension to the orbital apex. Tumours, such as nasopharyngeal cancers, trauma, infections, e.g. epidural abscesses (see below) and mucormycosis spreading from a paranasal sinus and inflammatory disorders (e.g. sarcoidosis and Wegener's granulomatosis, Chapter 25) are other causes.

Cavernous sinus syndrome

This can be clinically indistinguishable from the SOF syndrome except that V_2 as well as V_1 may be involved in the cavernous sinus syndrome. Proptosis does not occur, except in the case of carotid cavernous fistulas (Chapter 13). Involvement of both the oculomotor nerve and the sympathetic supply to the eye may result in a mid position, non-reactive pupil, or the pupil may be dilated or miotic because of parasympathetic or sympathetic involvement in isolation. There are a wide variety of possible pathologies including tumours (metastases particularly, but also meningiomas, nasopharyngeal carcinoma and lateral extension of pituitary tumours), aneurysms of the intracavernous portion of the carotid artery, carotid cavernous fistula, and granulomatous and inflammatory disorders, including the Tolosa–Hunt syndrome (Chapter 13). Cavernous sinus thrombosis is a serious condition that can follow infection of the face, paranasal sinuses (particularly the sphenoid sinus) or teeth. Spread to the opposite cavernous sinus usually occurs within a short time. The cavernous sinus syndrome is also discussed in Chapter 13.

Nuclear Vth nerve lesions

As with other cranial nerves, trigeminal nuclear lesions resulting from intrinsic brainstem pathology, such as tumour, inflammatory or vascular lesions, frequently involve other brainstem structures. Because the lateral spino-thalamic tract (that has already decussated) lies close to the trigeminal spinal tract and its nucleus, a common pattern is ipsilateral facial dissociated sensory loss (pain and temperature) with contralateral dissociated sensory loss in the limbs and trunk. Infarction of the lateral medulla (Wallenberg's lateral medullary syndrome; Chapter 4) is the most common cause.

The spinal trigeminal nucleus may be disrupted anywhere in the long course between the caudal pons and upper cervical cord. The somatotopic arrangement of the nucleus maps to an onion skin type distribution in the face, the nose and mouth being the centre of the onion, represented rostrally, with subsequent more posterior layers being more caudal in the nucleus (Figure 12.2). Thus, pontine nuclear lesions may result in intra-oral sensory loss with sparing of the face, while lesions of the lower part of nucleus (e.g. in syringobulbia) may be like a balaclava, sparing the muzzle area. The extension of the lower trigeminal spinal nucleus into the upper spinal cord means that lesions in this area may occasionally be a cause of facial pain and sensory disturbance.

Dorsal mid pons lesions involving the principal sensory nucleus and motor nucleus cause ipsilateral facial hemianaesthesia, usually to both light touch and pain/temperature, with paresis of muscles of mastication. There may be contralateral hemiplegia and spino-thalamic sensory loss in the limbs. Ipsilateral tremor, internuclear ophthalmoplegia and Horner's syndrome can also occur with lesions in this area. Dorsal mid pontine tumours can occasionally cause ipsilateral masticatory muscle spasm limiting jaw opening.

Trigeminal neuralgia

Trigeminal neuralgia (TN) is the most common disorder of the trigeminal nerve. Although not life-threatening, TN can be extraordinarily distressing. Prevalence is difficult to determine; incidence is approximately 4/100,000 per year. Women are more frequently affected than men. TN, often termed idiopathic but frequently caused by neurovascular compression, starts typically in the sixth and seventh decades; younger patients are more likely to have symptomatic TN, e.g. caused by MS, or occasionally a mass lesion.

Clinical features

The pain is usually quite characteristic, consisting of of excruciating lancinating paroxysms in the face. This pain is severe, often described as shooting, stabbing, electric shock-like or as like a red hot needle. Paroxysms last for a few seconds or a minute at most; they tend to occur in bouts, sometimes with such frequency that paroxysms become indistinct. Often a refractory period of several minutes is seen after each attack, the duration being proportional to the severity and length of the paroxysm. The face may contort during an attack, hence the name tic douloureux. Patients are usually pain-free between attacks but in some a superimposed dull background pain may develop, often a sign of a poor response to treatment. Sensory triggering of pain by touching a specific affected part of the face (often no larger than a few millimetres), or by talking, chewing, or even exposing the face to wind is very characteristic. Patients may be prevented from eating, drinking or brushing teeth; men may leave an area of the face unshaved. Weight loss can follow from pain triggered by eating. The mandibular and maxillary territories of the nerve are far more commonly affected than the ophthalmic division (only 5%); pain commencing in V_1 distribution should lead to consideration of an underlying cause for TN. Bilateral TN is rare (3%) and usually caused by intrinsic brainstem pathology such as demyelination.

Spontaneous remissions occur, lasting months or even years, but the pain almost always recurs. Successive bouts tend to be worse and more frequent, with shorter remissions and the pain may spread to affect a wider area of the face over time, typically commencing in V_3 distribution and moving to include V_2 and V_1. Patients may become fearful during a remission that the pain will return. Examination may be difficult as the patient may be hesitant to allow the face to be touched. Subtle areas of cutaneous sensory loss over the affected area are seen in a minority of patients if careful examination is performed, but examination is typically normal. The presence of other neurological signs points to an underlying cause for TN. Careful scrutiny of the teeth and oral cavity is important, to identify other causes of facial pain.

The diagnosis of TN is often made erroneously in patients with other causes of facial pain. The presence of characteristic paroxysms of lancinating pain is needed to make the diagnosis, supported by sensory trigger areas. The main differential diagnosis of TN is dental disease, particularly dental abscess and the cracked tooth syndrome, both of which can mimic localized forms of TN. Most patients consult a dentist initially, and many will have had dental work, with no improvement in pain, before the diagnosis of TN is suggested. Some will date onset of symptoms to a dental procedure. Acute glaucoma, sinusitis, giant cell arteritis and angina with referred jaw pain should all enter the differential diagnosis. Temporo-mandibular joint dysfunction causing facial pain is rarely like TN, usually associated with jaw movements and is probably over-diagnosed. Trigeminal autonomic cephalalgias such as cluster headache (Chapter 11) typically affect only the eye and surrounding area and usually easily differentiated from TN. Distinguishing V_1 TN from attacks of short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT; Chapter 11) can be more difficult. The occasional occurrence of facial rather than eye pain in SUNCT may lead to particular problems. A useful distinguishing feature is the duration of attack. This is typically less than 5 seconds in TN and 5 seconds to 5 minutes in SUNCT. The younger age of patients with SUNCT with the presence of prominent autonomic features, or the finding on imaging of a vascular loop in TN patients is helpful. Idiopathic stabbing headache (Chapter 11) may also enter the differential diagnosis of V_1 TN.

Atypical facial pain is frequently mistakenly labelled as TN initially. Unlike TN, atypical facial pain tends to be constant rather than paroxysmal, aching rather than lancinating, diffuse and poorly localized, often affecting the whole face and even areas outside the trigeminal territory. Trigger zones are usually absent. There is frequently associated depression or anxiety, although this does not necessarily imply a causal relationship.

Aetiology and pathogenesis

The main risk factors for apparently idiopathic TN are age and occasionally a history of hypertension. However, there is increasing evidence that in many cases, TN is caused by compression of the trigeminal nerve root at or near the dorsal root entry zone by an ectatic vascular loop, often of the superior cerebellar artery. Abnormal ephaptic non-synaptic transmission between trigeminal axons, within areas of focal demyelination caused by compression of the nerve has been proposed as the substrate of the pain, with increased excitability of the trigeminal–brainstem complex. High-resolution MRI studies demonstrate a distinct vascular loop in contact with the nerve in some cases. Other cerebellopontine angle masses including tumours (vestibular schwannomas, meningiomas, epidermoids) and aneurysms may sometimes compress the nerve.

Intrinsic brainstem pathology, particularly plaques of pontine demyelination in patients with MS, can cause symptomatic TN, which is occasionally bilateral. Patients with MS have a 20 times higher risk of developing TN. Up to 5% of patients with MS develop TN; occasionally TN is a presenting symptom of MS. Rarely, small infarcts in the dorsal root entry zone in the pons, or infiltration of the trigeminal nerve or ganglion by amyloid or tumour may lead to TN.

MRI is not essential in typical cases of TN, although increasingly carried out. Imaging is indicated where a symptomatic cause is suspected, e.g. in younger patients, in those with V onset of pain, abnormal examination findings or when surgical treatment such as microvascular decompression is contemplated.

Treatments

Until the advent of modern treatments patients were sometimes driven to suicide by the severity and distress of TN pain. A variety of effective medical and surgical treatments now exist, but evidence supporting their use is often observational rather than based on rigorous data.

Carbamazepine has been the first line drug for TN and it is effective or partially effective in 70% of cases. In practice, the problem is often achieving an effective therapeutic dosage quickly enough; side effects are often encountered in elderly patients when rapid titration regimes are used. Oxcarbazepine is used increasingly as a first or second line drug. It is as effective as carbamazepine and can be increased to an effective therapeutic dosage more rapidly and is often better tolerated. Other agents used alone or in combination include lamotrigine, baclofen, gabapentin and a variety of other anticonvulsant drugs. Conventional analgesics are not effective.

For patients with drug-resistant TN, or where drugs are not well tolerated, various surgical approaches are available. In general, surgery tends to be more effective than medical therapy. There is an increasing trend towards early surgical intervention, because sustained remission is the exception and natural history studies indicate TN often becomes gradually more severe and resistant to medical therapy. About half of all TN patients will require surgery.

Gasserian ganglion ablative techniques

These techniques involve selective ablation of part of the trigeminal ganglion, using a percutaneous approach via the foramen ovale, by radio-frequency thermocoagulation, glycerol or balloon microcompression. These procedures, performed as day cases or with a short in-patient stay, have a low morbidity and immediate efficacy. However, some degree of postoperative facial sensory loss is almost inevitable and they may provide only temporary relief. Late recurrence is common. The extent of sensory loss is proportional to long-term efficacy; those with minor sensory loss tend to have recurrence of pain. Radio-frequency thermocoagulation is the most common modality used, destroying a selected part of the ganglion within Meckel's cave. Analgesia lasts on average 2 years and the procedure can be repeated. Glycerol injection is a simpler technique, usually with earlier recurrence, but has fewer problems with postoperative numbness and pain than radio-frequency thermocoagulation. Anaesthesia dolorosa, the distressing and sometimes very painful dysaesthesia in an anaesthetic area, occurs in around 1% of patients treated by ablation techniques; it is resistant to treatment.

Microvascular decompression

This intracranial micro-neurosurgical procedure involves a general anaesthetic and the exposure of the trigeminal nerve at the brainstem. In some instances a vascular loop is seen to be compressing the nerve; the vessel is dissected away from the nerve and compression relieved, using Teflon felt or other material as a cushion. Decompression has a high long-term success rate, approximately 90% in published series, and has few frequent unwanted effects. Nevertheless, it is an intracranial procedure and carries a small risk of damage to other cranial nerves, especially unilateral deafness, as well as CSF leakage (2–5%) and, occasionally, cerebellar venous infarction.

Gamma knife radio-surgery

High doses of focused irradiation are directed at either at the root exit zone or the nerve itself within the pontine cistern, proximal to the Gasserian ganglion. Success rates for pain relief are reasonable, but this is usually delayed for several months. Long-term results and complications are not yet known.

Choice of surgical technique

Ganglion ablation techniques are most appropriate for the elderly and infirm. For those able to undergo microvascular decompression, this is certainly the preferred option for V_1 TN, where post-ablation corneal anaesthesia can lead to keratitis, and for TN patients generally who prefer a more definitive procedure with a low risk of facial sensory loss. Symptomatic TN caused by MS is generally treated with medical therapy initially; ganglion ablation techniques are the preferred surgical technique, but decompression may be remarkably effective in some patients (40%) even in the absence of an identifiable vascular loop.

Trigeminal sensory neuropathy

Facial sensory loss in the absence of a defined lesion of the trigeminal nerve or its central connections is usually described as idiopathic trigeminal sensory neuropathy and is probably a heterogeneous disorder.

Patients develop gradually evolving facial numbness, often preceded by positive sensory symptoms such as tingling, but usually without significant pain. In many cases initial symptoms are localized, typically in a circumoral distribution, with disregard for the divisional boundaries of the nerve. Gradual spread to involve the rest of the face, and sometimes the opposite side, is usual over a period of months or years. Tactile, temperature and pain sensation are usually diminished and taste sensation becomes impaired in the anterior two-thirds of the tongue in many. The corneal reflex is usually diminished or absent in those with V_1 involvement; the blink reflex may be delayed or absent in neurophysiological recordings in some but not all patients. The motor root is very rarely affected. A small subgroup have acute onset of sensory loss; this may represent a condition likened to Bell's palsy.

The association with autoimmune connective tissue diseases (CTDs) sometimes offers a clue to an underlying cause. Three conditions account for more than 90% of the CTDs associated with trigeminal neuropathy: undifferentiated connective tissue disease (47%), mixed connective tissue disease (26%) and scleroderma (19%). The condition is also seen in association with primary Sjögren's syndrome. Trigeminal neuropathy is seldom seen in the more common CTDs such as rheumatoid arthritis and systemic lupus erythematosus (SLE), and where it does occur in association with these disorders, is more likely to be acute in onset with systemic and other neurological involvement because of vasculitis. In a minority of patients, facial numbness develops before other rheumatological or systemic symptoms. Vasculitic damage to the trigeminal ganglion may explain trigeminal neuropathy in some cases without evidence of a CTD and there is speculation that tissue-specific autoimmune damage may explain some idiopathic cases.

Neuroimaging is usually normal. There are few pathological studies but the available evidence indicates a destructive inflammatory process at or near the Gasserian ganglion.

Generally, symptoms do not improve with time but few patients are severely disturbed by their symptoms, particularly once more serious neurological disorders have been excluded.

Non-specific, often intermittent, facial sensory symptoms are common in neurological practice, sometimes accompanied by sensory symptoms elsewhere in the body, and may sometimes be a feature of somatization (Chapter 21). Non-organic patterns of sensory loss are typical; examination is normal. Investigations are negative. Distinguishing such patients from patients with trigeminal sensory neuropathy is usually possible on clinical grounds.

Herpes zoster ophthalmicus

The lifetime risk of herpes zoster ophthalmicus (HZO) is about 1%. The other divisions of the trigeminal nerve are rarely affected. Elderly and immuno-compromised individuals are particularly at risk. Early ocular and later neurological complications are common and potentially serious.

As with shingles elsewhere, pain and sensory disturbance often precedes appearance of vesicles. Vesicles over the side of the nose and medial to the eye indicate involvement of the nasociliary nerve and predict involvement of the eye itself (Hutchinson's sign). Most patients with HZO have conjunctivitis. Without antiviral therapy 50% of HZO patients will develop severe ocular complications, including keratopathy, episcleritis, corneal perforation and iritis, some of which result – potentially – in blindness. Corneal anaesthesia may lead to secondary damage to the eye. Retinal necrosis may occasionally occur in immunocompromised patients.

All patients with HZO should receive oral antiviral therapy with aciclovir, valaciclovir or famciclovir as early as possible. The newer antiviral drugs may improve compliance, because dosing is three times daily rather than five times daily as with aciclovir. Treatment within 72 hours reduces the frequency of ocular complications from 50% to 20–30% and may reduce the duration of zoster-associated pain. Patients with eye involvement should be assessed by an ophthalmologist. Topical steroids may be indicated where there is anterior chamber inflammation. Taping of the lids is often helpful at night. There are some suggestions that steroids (oral and/or intravenous) in combination with antiviral drugs reduce the duration of pain and accelerate healing but there is no effect on the incidence of post-herpetic neuralgia (PHN). Steroids are not used routinely.

PHN is pain persisting more than 3 months after the rash. This is the most common neurological complication of HZO. Overall, 7% of patients with shingles have PHN at 3 months and 3% at 1 year. PHN is much more common in the elderly, in whom HZO usually occurs, and 20% of HZO patients over the age of 60 years develop PHN, with 9% persisting at 1 year. However, after allowing for age, patients with HZO are no more likely to develop PHN than those with shingles affecting other dermatomes. Treatment of PHN is usually with tricyclic antidepressants, e.g. amitriptyline, or anticonvulsants, sometimes in combination. Topical capsaicin cream may also be helpful. PHN may be refractory to treatment and have a major impact on quality of life.

Rarer late neurological complications of HZO include cranial nerve palsies (optic neuropathy and III, IV and VI) and stroke as a result of granulomatous arteritis of the intracranial carotid artery or its branches, probably caused by direct viral invasion of the vessel. This usually develops 1–2 months after the rash.

Atypical facial pain

Atypical facial pain is a residual diagnostic category for otherwise unclassifiable facial pain without an apparent structural cause. The features are of chronic facial pain, lasting months to years, usually unilateral and within trigeminal distribution, but without signs of Vth nerve sensory loss. The pain is described as deep and burning in quality. Paroxysms and trigger areas are typically absent. There have often been incorrect diagnoses, and invasive diagnostic or therapeutic procedures, sometimes multiple.

Patients are typically over 50 years of age, and predominantly female. Depressive features are prominent. Judgements have been have made that these patients are melancholic, obsessive and over-conscientious, and that this in some way is the cause of the pain. The reality is that there is no doubt that the condition exists, but there remains uncertainty about its aetiology. Of note, patients with atypical facial pain appear to have little in the way of other unexplained pain. Investigation is negative. Treatment, with tricyclic antidepressants and other similar drugs, although sometimes helpful, is frequently distinctly unsatisfactory. Attempts at invasive treatment usually cause the pain to increase.

VII. Facial nerve

The facial nerve has a long and complex course and may be damaged at any point. Bell's palsy is seen commonly in primary care, at all ages, and worldwide.

Functional anatomy

The facial nerve has motor, sensory and autonomic components and a tortuous course from pons to extracranial innervation of facial muscles, lacrimal and salivary glands, and visceral and somatic sensory territories. The anatomy is described in more detail in Chapter 2.

The majority of the upper motor neurone cortico-bulbar fibres decussate in the pons but the upper third of the face is said traditionally to receive bilateral cortical innervation, resulting in sparing of the brow and frontalis muscles with supranuclear lesions, e.g. after a stroke. The situation is more complex; the upper part of the face probably receives relatively little direct cortical innervation. Separate supranuclear anatomical pathways subserve voluntary and emotional facial movements; as a result these movements may be dissociated. Thus, emotional movements such as smiling, which are separate from the internal capsule pathway, may be preserved when voluntary movements are affected following a stroke. The right cerebral hemisphere is dominant for expression of facial emotion.

The VIIth motor nucleus lies in the lower pons. The fascicle of efferent motor fibres travels backwards, before sweeping around in a U-turn around the VIth nerve nucleus, to emerge anteriorly from the lower border of the pons.

The nervus intermedius is the distinct sensory and autonomic component of the facial nerve that joins the motor fibres just after the internal genu (Chapter 2; Figure 12.3). After leaving the pons, the facial nerve traverses the cerebellopontine angle before entering the internal auditory meatus of the temporal bone with the nervus intermedius and VIIIth nerve. The facial nerve emerges from the skull via the stylomastoid foramen. After traversing the parotid gland the nerve divides into several branches that innervate the facial muscles, with the exception of the levator palpebrae superioris, supplied by the IIIrd nerve – which explains why facial palsy does not cause ptosis, but instead widens the palpebral fissure (Figure 12.4).

Examination

Facial symmetry should be inspected, particularly forehead creases and nasolabial folds, remembering that a proportion of the normal population have some degree of facial asymmetry. Facial myokymia, synkinesis or hemiatrophy may be observed on careful inspection at rest and during facial movements. When

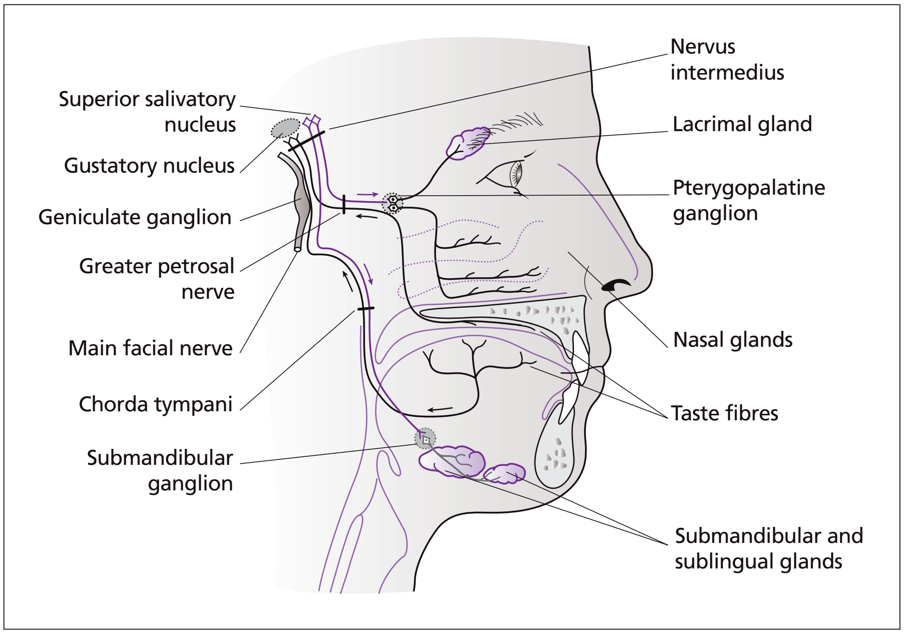

Figure 12.3 Nervus intermedius and its connections.

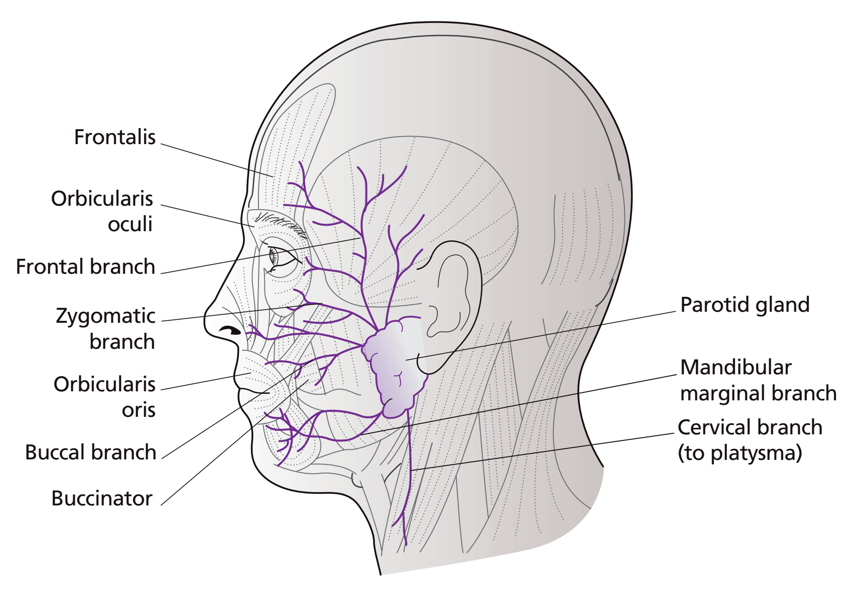

Figure 12.4 Principal facial branches of VIIth nerve.

assessing power, test frontalis (eyebrow elevation), as well as eye closure, lip closure and emotional facial movements such as smiling. Platysma is tested by asking the patient to bare their teeth and open the mouth at the same time. Asking the patient to blow out the cheeks and whistle are also useful. For patients with facial weakness, Bell's phenomenon (Chapter 3) is assessed. The ability to close the eye to protect the cornea needs to be examined specifically, to avoid exposure keratopathy. Upper motor neurone lesions produce relative sparing of the frontalis and orbicularis oculi muscles because of their bilateral innervation; voluntary and emotional movements may be affected differentially. Unilateral upper motor neurone facial weakness is often less evident to patients and relatives than lower motor neurone weakness. Gradual onset weakness or even bilateral facial weakness is less noticeable than sudden unilateral weakness.

The four primary tastes – sweet, salt, sour and bitter – can be tested using sugar, salt vinegar and quinine dabbed separately on to the tongue, rinsing the mouth between each test substance. In cases of facial weakness, examination should include inspection of the oral cavity, tongue and external auditory meatus for vesicles indicating zoster or for evidence of nasopharyngeal carcinoma or fissured tongue (lingua plicata). The parotid should be palpated for evidence of tumour, infection or inflammation. Otoscopic examination of the external auditory canal and tympanic membrane should be performed to look for evidence of infection or cholesteatoma.

Supranuclear facial weakness

Facial weakness caused by lesions of the upper motor neurones innervating the facial nucleus, e.g. following hemispheric stroke, are usually associated with ipsilateral limb weakness. In the face, the usual pattern is of relative sparing of the upper muscles because of their bilateral cortical representation and the fact that the cortical representation of the upper face is in the anterior cingulate gyrus rather than the motor cortex. Dissociation between voluntary and emotional facial movements may be seen; impairment of voluntary movement with relative sparing of emotional facial movements is more common than the converse.

In disorders such as progressive supranuclear palsy, disruption of supranuclear and brainstem mechanisms relating to facial movements may cause apraxia of eyelid opening; patients cannot voluntarily open eyes despite absence of overt facial weakness.

Nuclear VIIth lesions

Vascular, inflammatory and occasionally infiltrative brainstem lesions can affect the facial nerve nucleus within the pons or the intrapontine fascicle. This produces a lower motor neurone type facial palsy. This rarely occurs in isolation and like most brainstem lesions usually involves adjacent structures. The VIth nerve nucleus, around which the facial fasciculus sweeps, is often involved producing facial weakness and diplopia because of paralysis of lateral rectus on the same side. An associated contralateral hemiplegia (Millard–Gubler syndrome) is often caused by pontine vascular lesions; an ipsilateral gaze paresis reflects involvement of the paramedian pontine reticular formation.

Cerebellopontine angle syndrome

The petrous temporal bone, lying laterally, completes the triangular recess between the cerebellum and the lower border of the pons. The Vth nerve lies at the upper corner of the cerebellopontine angle (CPA), the IXth and Xth nerves at the lower, and the VIIth and VIIIth nerves between them (Figure 12.5). Mass lesions

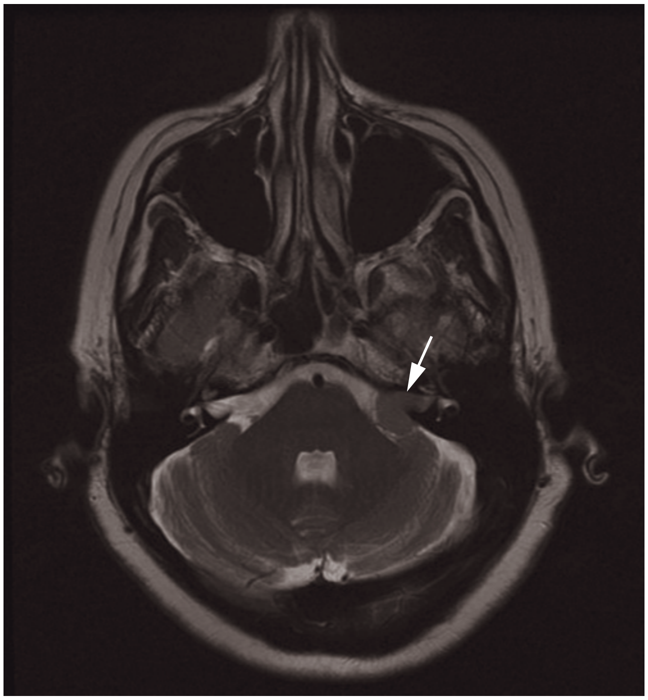

Figure 12.5 Vestibular schwannoma (MRI T2W).

in the CPA cause combinations of an VIIIth nerve lesion, a Vth nerve lesion and a VIIth. Additional features develop when the adjacent cerebellar lobe is damaged, and occasionally a IXth nerve lesion, upper motor neurone signs in the limbs and exceptionally hydrocephalus with papilloedema. VIIIth nerve schwannoma (acoustic neuroma; Chapters 14 and 20) is the typical cause. Meningioma, cholesteatoma, metastasis or occasionally an aneurysm can also produce a CPA syndrome.

With an VIIIth nerve schwannoma there is a typical but not invariable sequence. High-pitched tinnitus, at first intermittent, is followed by progressive sensori-neural deafness. Episodes of vertigo follow. Trigeminal facial sensory loss develops; initially this is symptomless – hence the importance of testing the corneal reflex. Facial weakness of lower motor neurone type follows. An IXth nerve lesion may be found. Later, as the tumour enlarges, cerebellar and other signs of brainstem involvement become apparent. In the elderly, when hearing loss has been neglected, hydrocephalus with raised pressure can be the presenting feature.

CPA lesions were sometimes hard to diagnose before the era of high-definition imaging but standard MRI sequences identify the great majority of CPA lesions.

Facial canal syndrome

At the internal auditory meatus the VIIth nerve lies close to the VIIIth, and may be affected with it. Damage to the nerve within the facial canal is common and it is here that the VIIth nerve is believed to be affected in Bell's palsy. The first (labyrinthine) portion of the facial canal is the narrowest and the only segment lacking anastomosing arterial arcades, making it vulnerable to ischaemia and compression at this point. The clinical picture will depend on where within the canal the lesion occurs. Damage proximal to the first branch of the VIIth nerve, the greater superficial petrosal nerve to the lacrimal gland, will result in facial palsy with loss of lacrimation, hyperacusis (nerve to stapedius) and loss of taste in the anterior two-thirds of the tongue (chorda tympani). Lesions distal to the origin of the nerve to stapedius will not cause hyperacusis, and those distal to the chorda tympani will spare taste.

Head injury may cause damage to the facial nerve within the facial canal, usually as a result of a transverse fracture of the temporal bone. After the olfactory nerve, the facial nerve is the cranial nerve most commonly involved in head trauma. Surgical decompression and use of steroids are sometimes advocated but there is little evidence to support their use. Malignant otitis externa in diabetic patients, usually caused by *Pseudomonas* infection, and suppurative middle ear infection may spread to adjacent tissue and the skull base resulting in facial palsy. Temporal bone metastases, nasopharangeal carcinoma and other tumours as well as disorders such as osteopetrosis and cholesteatoma may sometimes affect the facial nerve in this segment.

Lesions at and distal to the stylomastoid foramen

The facial nerve or its branches can be damaged at or distal to its exit from the skull at the stylomastoid foramen. Parotid tumours or inflammatory parotitis resulting from infection or granulomatous disease such as sarcoidosis may cause facial palsy. Individual branches of the nerve may be damaged by surgery to the parotid or face, carotid endarterectomy, facial trauma or carotid dissection. Misplaced botulinum toxin injections, for cosmetic purposes or hemifacial spasm, may also result in localized, but temporary, facial weakness.

Bell's palsy

Bell's palsy is an acute peripheral facial palsy. A large retrospective study of almost 2500 cases presenting to UK GPs showed an incidence of 20/100,000 per year. Bell's palsy may occur in childhood; incidence increases steadily with age. There is no change in incidence with season, latitude or geography and no evidence for familial clustering. Weak associations may exist with diabetes and hypertension. A viral aetiology has been postulated on the basis that decompression of the nerve in the acute phase usually reveals swelling of the facial nerve proximal to the geniculate ganglion, a finding confirmed by MRI, and detection of herpes simplex virus type 1 (HSV-1) DNA in endoneurial fluid in most patients. Both primary HSV-1 infection and reactivation of latent infection have been implicated. Microvascular ischaemic mononeuropathy of the facial nerve may also be causal in older patients. Bell's palsy has also been reported after immunization. Bell's palsy should no longer be considered idiopathic.

Clinical features

The clinical picture is stereotyped and familiar to most clinicians. Rapid onset of facial weakness progressing over 48 hours (and occasionally up to 5 days) is preceded or accompanied by diffuse retro-auricular pain in the region of the mastoid. In some patients, mastoid pain may be severe and persist for a week or longer. Facial weakness and asymmetry with drooling of liquids from the corner of the mouth on the affected side often lead the patient to suspect a stroke; most patients present promptly to primary care physicians. Not infrequently, patients mistakenly report that the contralateral unaffected side is the weak side. All facial muscles are usually equally affected. The palpebral fissure is widened on the affected side, eye closure and blinking are reduced or absent (with a visible Bell's phenomenon on attempted eye closure). Ectropion formation may lead to overflow of tears on to the cheek. The angle of the mouth droops with reduction of the nasolabial fold, smoothing of skin wrinkles; the platysma muscle is also involved. The extent of maximal facial weakness is variable, but is severe in the majority, although occasionally patients present with very mild facial weakness. For example, this may be noticed only because the patient is unable to form an adequate embouchure to play a wind instrument. However, a mild, painless, progressive or patchy facial weakness developing over several weeks is distinctly unusual in Bell's palsy, and suggests an underlying cause.

A vague alteration of sensation on the affected side of the face is relatively common in Bell's palsy, although the corneal reflex is preserved. Loss of taste, often described as a muddy or metallic taste, and hyperacusis (because of paralysis of stapedius) indicate involvement of the chorda tympani and the branch to stapedius, respectively.

Other causes of acute facial paralysis should be considered. The Ramsay-Hunt syndrome caused by varicella-zoster reactivation in the geniculate ganglion may be diagnosed by careful inspection of the external auditory meatus and palate for vesicles in these small somatic sensory territories of the facial nerve. Vesicles may be absent in some patients – zoster sine herpete. Other symptoms are common in the Ramsay-Hunt syndrome including tinnitus, hearing loss and nystagmus, indicating involvement of the VIIIth nerve and occasionally involvement of other cranial nerves such as the IXth and Xth. The ear should be examined for evidence of local pathology such as cholesteatoma or malignant otitis externa, and parotid tumours excluded. Lyme disease may possibly account for one-quarter of cases of facial palsy in endemic areas. Acute VIIth nerve lesions are sometimes seen at HIV seroconversion. A skull base tumour, such as a breast cancer metastasis, can also cause an isolated VIIth nerve lesion, sometimes with post-auricular pain.

Investigation

Investigations are not required in typical cases. MRI may show contrast enhancement of the distal intra-canalicular and labyrinthine portions of the facial nerve. Imaging is not routinely indicated, unless a brainstem or other cause is suspected. Gradual onset of facial weakness over weeks, presence of other neurological signs or failure to recover within 6 months should prompt further investigation, including imaging. In areas of high HIV prevalence, acute facial weakness is more often because of HIV seroconversion than the typical Bell's palsy seen in largely HIV-negative populations. In areas of high Lyme disease prevalence, testing for *Borellia* serology is appropriate.

CSF examination is not indicated in Bell's palsy; CSF constituents are normal.

Neurophysiological stimulation of the facial nerve with measurement of facial compound motor action potential 3–20 days after onset may identify those with severe Wallerian degeneration of the nerve and a correspondingly poor prognosis for recovery. In practice this is rarely required.

Management and outcome

Complete or almost complete recovery, without recurrence, over 3–8 weeks is the norm in at least 85% of cases, even without any treatment. Reassurance about the good prognosis and absence of recurrence is important. Inability to blink in severe facial weakness may lead to exposure keratitis and early evaluation should include assessment of the eye. Lubricating eye drops are often required and patients should be shown how to tape the eye closed at night. Severe facial weakness with complete inability to close the eye requires urgent ophthalmological assessment; lateral tarsorrhaphy and/or temporary insertion of a gold weight into the upper lid may be necessary.

Early treatment with steroids and antiviral agents remains contentious although this is now near standard practice. Some studies indicate a better outcome with steroids but a rigorous analysis as part of a Cochrane review concluded that there was insufficient evidence to support the use of steroids. Nevertheless, many clinicians choose to treat patients with oral prednisolone (typically 1 mg per kg for 7 days) if they present within a week of onset. Evidence to support use of antiviral agents is even more limited; one randomized trial showed a better outcome with an aciclovir–prednisolone combination than prednislone alone. Another found no advantage for either aciclovir alone or in combination with prednisolone, and recommended that aciclovir should not be used in most clinical situations. However, treatment with an aciclovir–steroid combination could be justified on the basis that HSV reactivation may be a frequent cause of Bell's palsy, and that some cases of Ramsay Hunt syndrome may occur sine herpete.

Surgical decompression of the labyrinthine portion of the facial nerve in the acute phase has had its proponents, but there is little evidence to support this practice – now rarely performed in the UK. Over 80% of UK patients with Bell's palsy are managed in primary care; most receive no medical treatment.

The extent of early weakness is an important prognostic sign, with incomplete facial weakness indicating a better prognosis than total paralysis. For the majority of patients where recovery occurs within several weeks, conduction block and segmental demyelination, with intact axonal integrity within the facial canal, is presumed to be the basis of facial weakness. Where axonal loss and Wallerian degeneration have occurred, recovery follows after axonal regrowth. This is delayed by 4–6 months, or even longer. In these cases, recovery is usually incomplete, particularly for the more distal branches supplying the brow and mouth, and often associated with contracture or tightness of facial muscles. Aberrant reinnervation of facial muscles and glands is common in late recovery, leading to synkinesis and the phenomenon of jaw-winking – involuntary eye closure with lip or mouth movement, known as the inverse Marcus Gunn phenomenon or Marin Amat syndrome. Similarly, lip movement may occur on blinking. Aberrant parasympathetic reinervation may lead to watering of the eye when eating (crocodile tears), caused by misdirection to the lacrimal gland of fibres destined for the submandibular salivary glands. This complication may be successfully treated with botulinum toxin injections to the lacrimal gland.

For the minority left with severe facial weakness after a year, reconstructive facial surgery can be helpful. A variety of procedures may be considered: botulinum toxin for synkinesis, and into the contralateral side of the face to rebalance the cosmetic appearance, and highly specialized surgical procedures such as reanimation. The latter involves sural nerve grafting of a branch of the contralateral facial nerve, the aim being to innervate the paretic side. After 6 months (to allow axonal growth along the sural graft), this is followed by insertion of a revascularized pectoralis muscle flap into the affected side to improve function. In some patients, particularly older people, a simple muscle sling procedure improves cosmetic appearance, without improving movement.

Recurrent facial palsy

Bell's palsy is rarely recurrent (it is so in <5% of cases) and should in any event prompt a search for an underlying cause, such as sarcoidosis. However, if a recurrent facial palsy occurs without evidence of other pathology, Bell's palsy is the likely answer.

Melkersson–Rosenthal syndrome

This condition is a rare triad of intermittent VIIth nerve palsy, persistent or recurrent lip or facial swelling, and a fissured tongue (lingua plicata*)*. The facial paralysis is identical to Bell's palsy, but has a distinct tendency to recur, and may be bilateral. These features are diagnostic clinically. Characteristic non-caseating granulomas are found on lip biopsy; the lip swelling is sometimes treated with local steroid injections. The aetiology is entirely unknown.

Bilateral facial weakness

Bilateral facial palsy is rare, accounting for fewer than 1% of cases of facial palsy, and is much more likely to be a manifestation of a systemic disease than a unilateral palsy, isolated or recurrent. Paradoxically, patients with bilateral facial weakness are often slower to present than those with obvious facial asymmetry.

In one large case series, bilateral Bell's palsy was the most common cause of bilateral facial palsy. Infective diseases such as bilateral mastoiditis and diptheria have been replaced by HIV seroconversion, EBV infection and Lyme disease (Bannwarth syndrome) as a cause of bilateral facial weakness. Lyme disease facial palsy is bilateral in one-quarter of cases and may be associated with a facial rash and CSF pleocytosis. Bilateral facial weakness may be a presenting feature of sarcoidosis. Other causes include trauma with skull base fracture, pontine glioma, tumours including bone metastases, leukaemic deposits within the skull base and malignant meningitis. These tend to cause gradually evolving facial weakness.

Bilateral facial weakness may be a feature of a more generalized neuromuscular disease. This occurs commonly in Guillain–Barré syndrome and the Miller Fisher variant, and is also a feature of disorders such as myotonic dystrophy, facioscapulohumeral dystrophy (sometimes presenting years before weakness of shoulder girdle muscles), myasthenia gravis, botulism, various congenital myopathies and MND. Möbius syndrome is a congenital disorder characterized by bilateral facial weakness, usually in association with abducens palsy and other neurological deficits. A rare form of familial amyloid polyneuropathy caused by gelsolin gene mutations may cause bilateral facial palsy with corneal lattice dystrophy.

Hemifacial spasm

This is a benign, usually painless but often distressing condition, characterized by unilateral, involuntary, irregular tonic or clonic contractions of muscles supplied by the facial nerve. Prevalence is 14.5/100,000 and 7.4/100,000 in women and men respectively. Onset is usually in the fifth and sixth decades.

In some patients the involuntary movements start in the orbicularis oculi muscle and gradual progression over months or years to involve other facial muscles on the same side. In others, the problem begins with twitching around the mouth or the cheek. Movements are irregular in rhythm and degree but synchronous in all affected muscles. They may be spontaneous or triggered by voluntary facial movements including chewing and speaking, and they are made worse by stress or fatigue. Movements usually persist during sleep. Bilateral involvement is rare (3%), and when it occurs movements are never synchronous on the two sides. Examination is usually normal although subtle ipsilateral facial weakness is sometimes seen. It is now generally accepted that hemifacial spasm is usually caused by extrinsic compression of the root entry zone of the facial nerve, generally by vascular structures such as the vertebral or basilar arteries or their branches. Other mass lesions in the CPA, including tumours, are the cause in about 1% of cases. Secondary hemifacial spasm, following injury to the peripheral facial nerve or following Bell's palsy also occurs. High-resolution MRI with fine cuts through the region of the facial nerve root entry zone demonstrates a vascular structure in contact with the nerve in some cases. Imaging is not usually needed, except in atypical cases where onset is not around the eye, where there are abnormal findings on physical examination or when surgical treatment is being considered.

Botulinum toxin injection into affected muscles is now the first line for those patients who want treatment. Injections need to be repeated every 3–4 months and many patients eventually develop some degree of facial weakness and atrophy. Drug treatment with carbamazepine, gabapentin, clonazepam and baclofen are rarely very effective and seldom result in resolution of symptoms, certainly at tolerable doses. Microvascular decompression of the facial nerve in the posterior fossa involves interposing a non-resorbable sponge between the nerve and any adjacent vascular loop identified at operation. The procedure is sometimes claimed to give complete resolution of symptoms in some 60% of cases, but is associated with a risk of 3% facial weakness or 3% unilateral deafness.

Hemifacial spasm may occasionally occur with ipsilateral trigeminal neuralgia, one symptom usually preceding the other, a combination called tic convulsif. The paroxysms of pain and spasm occur independently. A compressive cause such as a vascular loop or other structural lesion is usually identified.

Other involuntary facial movements

Myokymia of orbicularis oculi, an irritating twitch usually of the lower eyelid, is a normal phenomenon, but sometimes a cause of anxiety. More extensive facial myokymia, with persistent worm-like wriggling of the chin and other facial muscles is more sinister. This is typically caused by intrinsic brainstem pathology such as MS, or a pontine glioma, in both cases it is usually progressive. Facial myokymia is also a hallmark of some inherited ataxias, particularly SCA3. Tics and tardive dyskinesia frequently involve facial or perioral muscles. Neuro-acanthocytosis may cause prominent oro-facial dystonia. Blepharospasm is a form of focal dystonia affecting orbicularis oculi (Chapter 5). Fasciculation of facial muscles can develop in motor neurone disease. Focal motor seizures may affect facial muscles alone in some cases; epilepsy partialis continua (Chapter 6) is a cause of persistent clonic–tonic facial movements, which can be localized and difficult to recognize.

Progressive hemifacial atrophy

Also known as Parry–Romberg syndrome, this rare and unusual condition consists of progressive hemifacial atrophy of skin, soft tissue and bone, sometimes with pathological changes within the brain. This begins in childhood, with gradual progressive atrophy, typically in one or more trigeminal nerve dermatomes. Facial sensation remains normal. There is no denervation. The condition is believed in some cases to be related to linear scleroderma. Sometimes a vertical fissure, known as a coup de sabre, separates atrophic areas from normal facial structures. Brain imaging shows ipsilateral grey and white matter lesions in some cases. Epilepsy sometimes occurs. The cause is unknown. There are suggestions that a chronic inflammatory process underlies the condition.

Lower four cranial nerves: IX, X, XI and XII

An outline of the peripheral course of these four nerves is shown in Figure 12.6. Their complex central arrangement and nuclei are summarized in Chapter 2.

IX. Glossopharyngeal nerve

Functional anatomy

The IXth nerve (Chapter 2) is predominantly sensory but also contains motor and parasympathetic components. It arises from the lateral medulla as a series of small rootlets rostral to those of cranial nerves X and XI. All three nerves then pass through the jugular foramen. At this point or just beyond, the IXth nerve divides into the superior and petrous ganglia, before descending the pharynx between the internal jugular vein and internal carotid artery. The small motor root supplies pharyngeal constrictors and elevators. The principal sensory root supplies taste and tactile

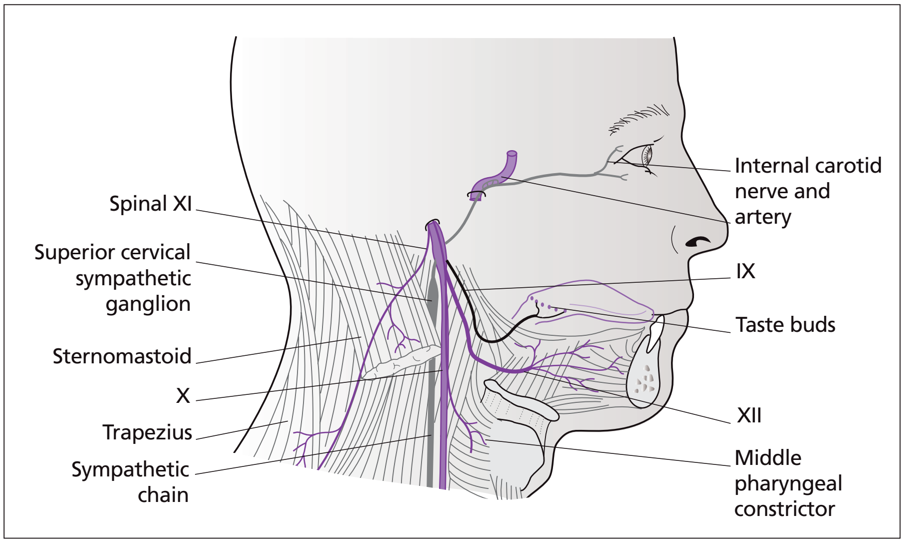
Spinal XI
Superior cervical sympathetic ganglion
Sternomastoid
X
Trapezius
Sympathetic chain
Internal carotid nerve and artery
IX
Taste buds
XII
Middle pharyngeal constrictor

Figure 12.6 Peripheral course of nerves IX, X, XI and XII.

sensation from the posterior one-third of the tongue, the posterior pharyngeal wall, Eustachian tube and tympanic membrane, and other targets such as the chemo- and baro-receptors. The parasympathetic fibres, from the inferior salivatory nucleus, leave the glossopharngeal nerve at the petrous ganglion running in the tympanic and petrosal nerves. They terminate in the parotid gland, via the auriculo-temporal branch of the trigeminal nerve.

Examination

Pharyngeal sensation can be tested with the end of an orange stick. In a IXth nerve lesion, there is altered sensation in the soft palate and pharynx. This is frequently difficult to diagnose in isolation, and rarely of great importance because other neighbouring nerves are also often affected. Loss of taste over the ipsilateral posterior third of the tongue is rarely symptomatic and cannot be tested. Isolated weakness of stylopharyngeus (which elevates the palate) is difficult to detect, with only mild dysphagia or asymmetry of the palatal arch at rest. Because the nerve supplies the afferent limb of both the pharyngeal and palatal reflex arcs, as well as the motor component of the former, a IXth nerve lesion has the potential to interfere with both these reflexes. Stimulating the normal pharynx, base of tongue or tonsillar area, with an orange stick, will result in pharyngeal elevation and constriction, with a degree of tongue retraction. In an isolated IXth nerve lesion the muscles of the pharynx supplied by the vagus continue to contract, making it impossible to diagnose an isolated IXth nerve lesion by this method.

IXth nerve lesions, peripheral and central

An isolated peripheral glossopharyngeal nerve palsy is excessively rare. Lesions can be generally identified by the additional structures involved. Central lesions: unilateral supranuclear lesions cause no deficit, because of the bilateral input to the nucleus ambiguous. It is only when there are bilateral corticobulbar lesions, as part of pseudobulbar palsy that overt signs are seen: including tongue spasticity and dysarthria, with emotional lability.

Peripheral lesions usually occur as part of the jugular foramen and CPA syndromes. More distally the nerve can be injured in the retropharyngeal space by structural lesions (e.g. a primary tumour such as nasopharyngeal carcinoma or metastatic spread) and surgical complications (e.g. carotid endarterectomy).

Glossopharyngeal neuralgia

Glossopharyngeal neuralgia is a rare condition. There is unilateral sharp stabbing pain in the ear or throat, lasting for seconds or minutes. Like trigeminal neuralgia, pain is triggered by movement of neighbouring structures, such as yawning or chewing. The pain is intense and paroxysmal. Bradycardia or even asystole with hypotension and syncope have been described in an attack. The cause often remains obscure, although CPA structural lesions, demyelination and possibly vascular loop compression of the posterior inferior cerebellar artery have been found. As with trigeminal neuralgia, carbamazepine and gabapentin may be effective. Microvascular decompression is usually curative. Nerve section is also sometimes carried out

X. Vagus nerve

Functional anatomy

The central origins and connections of the vagus and its relations to IX, XI and XII are outlined in Chapter 2. The vagus exits at the jugular foramen with the spinal accessory nerve and glossopharyngeal nerve. Two ganglia are formed (jugulare and nodose), and from this region a number of rami project: auricular (external ear), meningeal (posterior fossa dura mater) and pharyngeal (soft palate and pharynx). There are two principal laryngeal nerves, superior and recurrent, whose anatomy is shown in Figure 12.7. The vagus carries the parasympathetic supply to many thoracoabdominal organs, with fibres from the nucleus ambiguus innervating the striated muscle of larynx, pharynx and soft palate, with the exception of stylopharyngeus (IXth) and tensor veli palati (Vth). Sensory input from the viscera and taste from the palate and epiglottis are carried back to the nucleus solitarius.

Clinical features

Vocalization, swallowing and palatal movement are the major functions observable clinically. Bilateral lesions cause complete palatal, pharyngeal and laryngeal paralysis resulting in severe dysphagia, dysphonia and respiratory compromise with stridor, inability to cough and high risk of aspiration. Tracheostomy is usually required in acute bilateral nuclear or peripheral lesions, which may otherwise be life-threatening.

Unilateral vagus nerve palsy is characterized by dysphonia – the voice is hoarse and weak, with variable, usually mild, dysphagia. The vocal cords cannot be opposed, causing the cough to be weak and dependent upon forceful expiration; this is described as bovine. There is difficulty clearing the throat; the voice can often sound wet, because of pharyngeal pooling of secretions. Clinical examination demonstrates soft palate droop on the affected side; there is failure of elevation of the ipsilateral palate and the uvula may be pulled towards the unaffected side on phonation. Sensory examination is essentially impossible because of inaccessibility (meningeal structures) or co-innnervation (e.g. the pinna). Unilateral depression of the gag reflex occurs with a lesion of one vagus nerve. Autonomic dysfunction can occur and is discussed in Chapter 23.

Causes and localization of lesions

Major supranuclear lesions, e.g. acute hemispheric stroke, may cause transient swallowing difficulty, but the bilateral innervation of vagal brainstem nuclei means compensation usually occurs rapidly. Bilateral supranuclear lesions cause pseudobulbar palsy (see below). Nuclear lesions are usually accompanied by damage to adjacent structures within the medulla which may dominate the clinical picture. Vascular lesions of the vertebral artery or

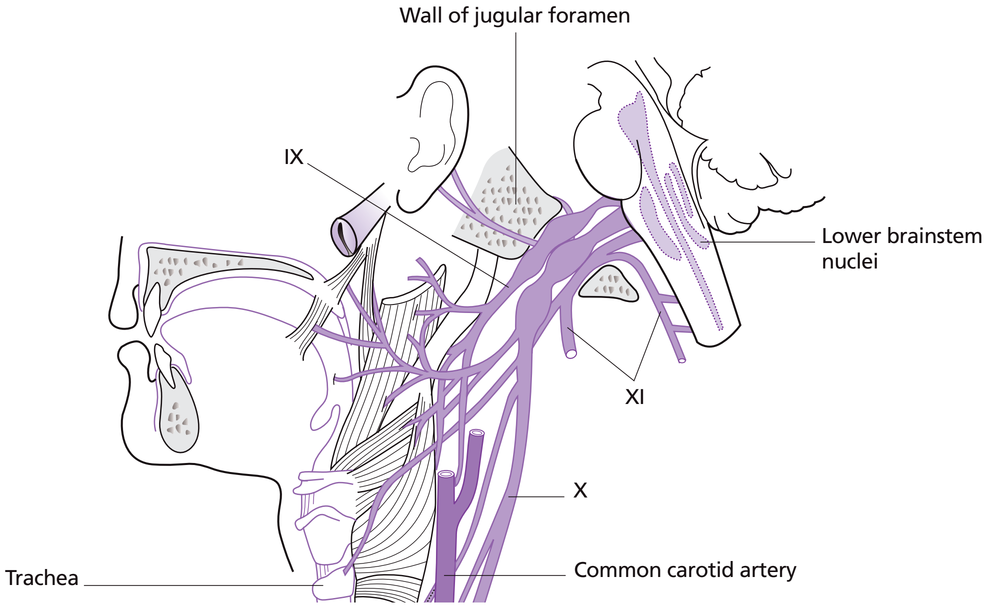

Figure 12.7 Scheme showing IXth, Xth, XIth nerves, skull base and brainstem.

its branches may cause a characteristic clinical syndrome of infarction of the lateral medulla – Wallenberg's lateral medullary syndrome (Chapter 4). Dysphagia and dysphonia because of involvement of the nucleus ambiguus are accompanied by vertigo, ipsilateral cerebellar signs, Horner's syndrome and spinothalamic sensory loss of the contralateral half of the body and the ipsilateral face. Other structural and inflammatory disorders in this region can also affect long motor and sensory tracts; there are a number of eponymous syndromes, e.g. Jackson's syndrome (vagus, XIIth nerve and corticospinal tract); Avellis' syndrome (vagus and spinothalamic tract; Table 12.1). Syringobulbia, motor neurone disease and vascular lesions can cause bilateral nuclear lesions affecting the vagus, producing a complete or partial bulbar palsy. Multiple system atrophy may affect the vagal nuclei causing stridor because of partial vocal cord paralysis as well as the autonomic disturbances characteristic of this condition.

Table 12.1 Eponymous syndromes involving the lower four cranial nerves.

	IX	X	XI	XII	Notes
Intrinsic					
Wallenberg	✓	✓	✓		With spinal V
Jackson		✓		✓	
Avellis		✓			± Horner's syndrome
Extrinsic					
Villaret	✓	✓	✓	✓	+ Horner's syndrome
Collet–Sicard	✓	✓	✓	✓	
Vernet (jugular foramen)	✓	✓	✓		
Tapia		✓	±✓	✓	
Hughlings Jackson		✓	✓	✓	
Schmidt		✓	✓		

Peripheral lesions in the extramedullary intracranial region and as the nerve exits the skull through the jugular foramen often involve the IXth, XIth and XIIth nerves. Primary tumours, e.g. chordoma, skull base or meningeal infiltration by metastatic tumour and inflammatory disorders, may all be responsible (see jugular foramen syndrome below). Extracranial lesions of the nerve trunk in the neck, where it runs in the carotid sheath, may result from carotid dissection, surgery or lymph node inflammation, e.g. tuberculous, at the skull base. More distally, beyond the point at which the pharyngeal nerve arises high in the cervical region, a complete isolated vagal palsy causes unilateral vocal cord palsy and laryngeal anaesthesia but spares pharyngeal and palatal muscles. The superior laryngeal nerve, which arises just distal to the pharyngeal nerve, is primarily sensory and lesions tend to be asymptomatic; classically cricothyroid dysfunction causes an inability to raise the vocal pitch, with a degree of hoarseness.

Lesions of the recurrent laryngeal nerve are more common than isolated vagus trunk lesions. These cause degrees of dysphonia, which may be transient if unilateral, or severe if bilateral. The left recurrent laryngeal nerve is more frequently involved than the right because of its longer intrathoracic course making it vulnerable to mediastinal lesions such as lung malignancy, left atrial enlargement and aortic arch aneurysm. A wide variety of pathological processes (e.g. thyroid masses, lymph node and oesophageal malignancy) can affect the recurrent laryngeal nerves as they ascend through the neck and they are vulnerable during thyroid and parathyroid surgery. In a significant proportion of cases, however, the cause of an isolated recurrent laryngeal nerve palsy remains undetermined, even after extensive investigation; spontaneous recovery may occur.

Investigation

This is based around comprehensive ENT evaluation, with appropriate MRI and CT imaging of brainstem, skull base, neck and upper thorax. If no structural pathology is identified, CSF examination may be needed. The clinical picture will help to localize the lesion and guide targeted investigation. In practice, when confronted with a patient with a vocal cord palsy, the clinician needs to establish if there is evidence of other brainstem signs or involvement of other lower cranial nerves and to look for associated pharyngeal and palatal paralysis.

XI. Accessory nerve

Functional anatomy

The spinal accessory nerve is the motor nerve to the upper portion of the trapezius and sternocleidomastoid muscles. Unusually, the XIth nerve has twin origins: the caudal portion of the nucleus ambiguus forms the internal ramus (minority), and the accessory nucleus of the upper cervical spinal cord (C1–6), the spinal root and external ramus (majority). The pathway begins by ascent of the spinal root through the foramen magnum and the nerve then exits from the skull via the jugular foramen (Figure 12.8). From there, the internal ramus supplies the larynx and pharnynx with the Xth nerve; the external ramus supplies the sternocleidomastoid and trapezius muscles. Strictly speaking, the fibres of the cranial root of the nerve destined to form the internal ramus are functionally and anatomically part of the vagus nerve; thus, the accessory nerve is primarily a spinal nerve with an intracranial course rather than a true cranial nerve. Afferent twigs from the cervical and thoracic nerves combine with spinal XI as it pierces trapezius – an anomalous arrangement (Chapter 2).

Examination and localization of lesions

The right sternomastoid is tested by asking the patient to turn the head to the left against resistance; both sternomastoids contracting together produce head flexion. The trapezius raises the abducted arm above horizontal, and is responsible for much of the scapular movement. This is tested by asking the subject to shrug their shoulders.

The clinical picture is relatively straightforward for unilateral peripheral lesions. The shoulder droops lower on the affected side, with wasting of the upper trapezius, accompanied by weakness of shoulder elevation and arm abduction above 90°. Winging of the scapular is seen, particularly when the arm is moved laterally, as opposed to damage of the long thoracic nerve when the winging is seen with forward movement of the arms against a flat surface, because of serratus anterior weakness. Isolated bilateral sternocleidomastoid lesions are extremely rare but generalized neuromuscular processes such as myotonic dystrophy, inflammatory myopathies, some muscular dystrophies and myasthenia gravis also affect these and other neck muscles and are a more common cause of neck flexion weakness.

With central hemispheric lesions, the trapezius is weak on the side of the hemiparesis, while the sternomastoid is weak ipsilateral to the cortical lesion (so head turning is weak towards the side of the hemiparesis). Dissociated weakness has also been described, mainly indicating brainstem or upper cervical pathology.

XIth nerve lesions

The leading cause of damage to the XIth nerve is iatrogenic trauma during operations such as lymph node biopsy in the posterior cervical triangle and other surgery in this region. Historically, tuberculosis of the neck was a major cause. Vascular procedures such as carotid artery endarterectomy and internal jugular vein cannulation are also well-recognized causes (Table 12.2).

These lesions cause weakness of trapezius but spare the sternomastoid. The trapezius weakness following XIth nerve lesions is sometimes associated with persisting severe local shoulder pain and/or deep pain in the trapezius, possibly caused by mechanical factors relating to shoulder droop and scapular winging, or to the anomalous afferents described above. Neurophysiology studies can confirm the site of the peripheral lesion, followed if needed by imaging. Surgical intervention has a distinct place in management, using direct grafting, end-to-end repair or neurolysis. There are also instances of spontaneous accessory neuropathy, perhaps allied to neuralgic amytrophy with pain in the lateral neck or shoulder, which subsides over several weeks followed by weakness and wasting. Recovery is rare. A recurrent variant has been described, with one individual experiencing two episodes over 8 years.

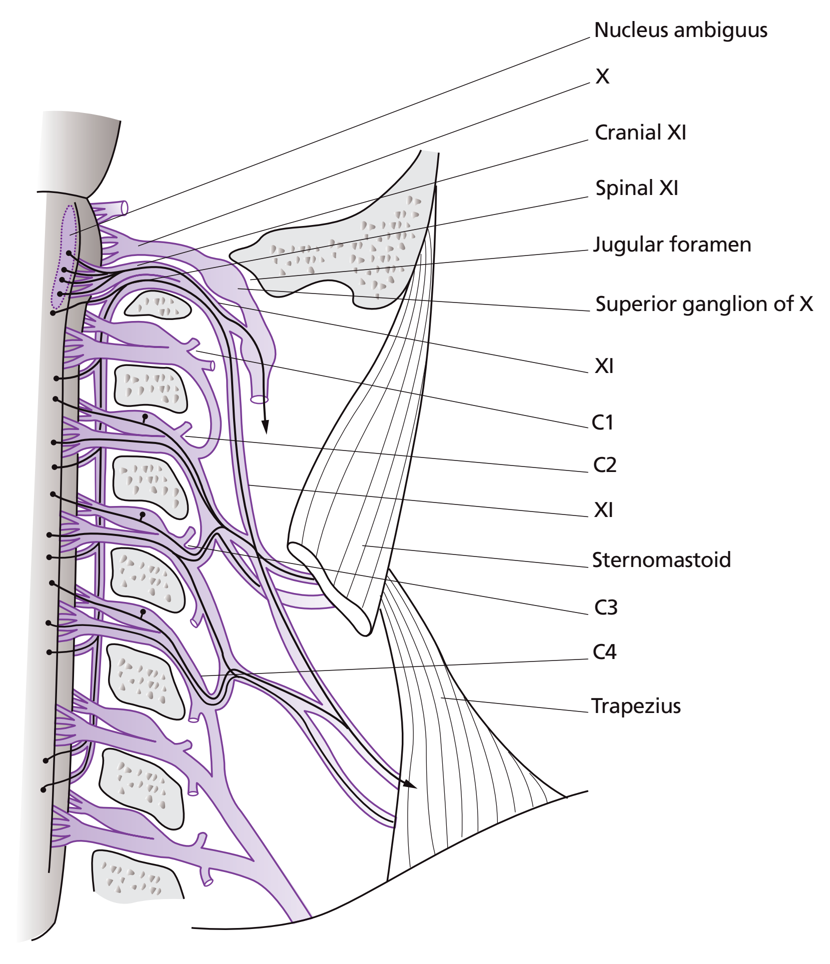

Figure 12.8 Jugular foramen, X and XI (AP, cord and medulla).

Table 12.2 Causes of accessory nerve lesions. (From Kim *et al.* 2003 with permission.)

Cause	No. of patients
Iatrogenic	
Lymph node biopsy	82
Tumour excision	19
Carotid endarterectomy	1
Plastic surgery face lift	1
Traumatic	
Stretch	5
Laceration	3

The spinal nucleus of XI may be affected by local structural and inflammatory cord pathologies. In the posterior fossa, the intracranial portion of the nerve can be damaged, often in combination with the glossopharyngeal and vagus nerves (Table 12.1; see jugular foramen syndrome).

XII. Hypoglossal nerve

Functional anatomy

Glossal muscles, both intrinsic and extrinsic, are supplied by the hypoglossal nerve; the peripheral route travelled is illustrated in Figure 12.9. The styloglossus elevates and retracts the tongue, the hypoglossus convexes and the genioglossus protudes the tongue. The nucleus is beneath the floor of the 4th ventricle, and the nerve emerges as a series of rootlets between the olive and pyramid, in the ventrolateral sulcus. In the posterior cranial fossa, the XIIth nerve exits the skull through the hypoglossal foramen, close to the jugular foramen. Its proximity to both the internal carotid artery and internal jugular vein is important.

Examination and localization of lesions

Observation of the tongue in both resting and active states is essential, the latter including forward–backward and side–side movements. A variety of signs of unilateral or bilateral wasting can be seen: furrowing, atrophy, fissuring, discoloration and

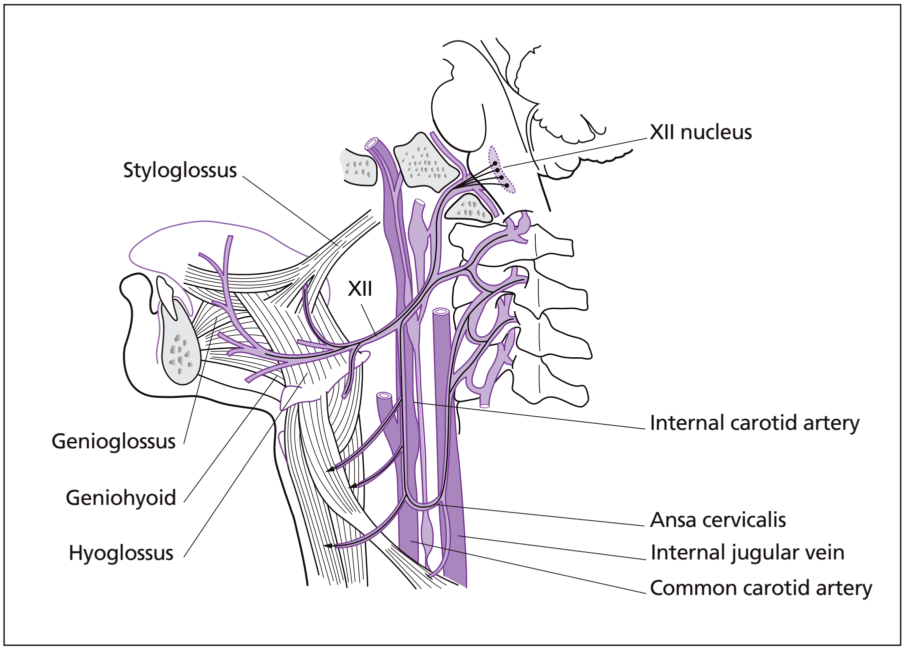

Figure 12.9 Peripheral distribution of XIIth nerve and other principal structures.

fibrillation. Tongue fibrillation, seen typically bilaterally in motor neurone disease, should only be diagnosed with the tongue at rest within the mouth; the normal tongue often has some flickering movements visible when protruded. Alternatively, the tongue can be spastic, with a small triangular appearance when protruded and slow clumsy movements (see pseudobulbar palsy below).

Peripheral pathology affecting one XIIth nerve cause the tongue to deviate to the side of the lesion on tongue protrusion. Subtle weakness is detected by asking the patient to press the tongue against the inside of each cheek (weakness is evident when the tongue is pressed against the cheek on the same side as the lesion). Typically unilateral wasting and atrophy follow.

Unilateral upper motor neurone lesions can result in deviation of the tongue contralateral to the lesion, without evidence of wasting, although caused by the bilateral representation; this is uncommon (Chapter 2). Bilateral lower motor neurone lesions result in an inability to protrude the tongue, mild dysphagia and severe dysarthria (see bulbar palsy, below)

Table 12.3 Causes of XIIth nerve lesions. (After Keane 1996 with permission.)

	Total (%)	Bilateral (%)
Tumour (metastatic, chordoma, nasopharyngeal carcinoma, lymphoma, acoustic neuroma, pontine glioma, glomus tumour)	49	18
Trauma	12	1
Stroke	6	1
Non-organic	6	0
Surgery	5	0
Multiple sclerosis	5	4
Infection	4	2
Guillain–Barré	4	3
Other	6	4
Unknown	3	0
Total	100	33

Causes of XIIth nerve lesions

Table 12.3 relates to a case series of hypoglossal nerve palsies gathered over a 26-year period. A variety of tumours account for half, mainly peripherally in the skull base or neck, with half of those being malignant, e.g. nasopharyngeal carcinoma, lymphoma and metastatic carcinoma. Nasopharyngeal carcinoma commonly involves the Vth and VIth nerves and can spread within the cavernous sinus to involve the IIIrd nerve. In another series of approximately 1000 patients with nasopharyngeal carcinoma, 22% presented with cranial nerve involvement, in which the XIIth nerve was involved in 19%, rising to nearly one-third at follow-up. Trauma is an important cause of XIIth nerve damage, in particular bullet, shrapnel and knife wounds. Damage from infection is rare but when there is evidence of sepsis, osteomyelitis of the clivus should be suspected, in particular in patients with diabetes who have *Pseudomonas* infection originating in the

Table 12.4 Common nerve lesions following carotid endarterectomy and stenting.

Nerve involved	Effect	Usual outcome
Cervical sympathetic chain	Horner's syndrome	Permanent
Hypoglossal (XII)	Tongue deviation	Recovery
Recurrent laryngeal (X)	Hoarseness, dysphagia	Variable
Cutaneous cervical branches	Sensory loss around neck	Some numbness: common
Accessory (XI) – unusual	Weak sternomastoid; pain	Variable

ear (malignant otitis externa). An isolated XIIth nerve lesion, usually associated with neck pain, is sometimes seen as part of carotid artery dissection (Chapter 4) and sometimes following carotid endarterectomy.

The proximity of the XIIth nerve to the other lower cranial nerves in the posterior fossa and neck has already been mentioned; combinations of cranial nerve palsies are frequently seen.

Investigation

Imaging of the skull base and neck is essential, predominantly using MRI and fine-cut CT, usually with contrast enhancement. If no cause is revealed, then CSF analysis looking for inflammatory and infiltrative causes may be needed. Electrophysiological studies can be useful, e.g. in motor neurone disease or Guillain–Barrré syndrome.

Cranial nerve injury following carotid endarterectomy

Cranial nerve injury is a common problem following carotid endarterectomy and, in the authors' experience, often understated to patients prior to surgery (Table 12.4). The nerve most frequently affected is the hypoglossal.

Jugular foramen syndrome

This pattern of IXth, Xth and XIth nerve lesions is known as Vernet's syndrome. Figures 12.8 and 12.9 demonstrate how structural disease at the jugular foramen can damage this trio of cranial nerves. As predicted, the presentation is dysphagia, dysphonia, sensory loss over the posterior third of the tongue, soft palate, pharynx and larynx (IXth and Xth) and ipsilateral sternomastoid/trapezius atrophy and weakness (XIth). Tumours arising in the locality include glomus tumours, meningiomas, neuromas, metastases and choleastomas. Chronic infective (e.g. varicella-zoster or *Pseudomonas*) and vascular processes (e.g. internal carotid artery dissection, giant cell arteritis and jugular vein thrombosis) can also cause the syndrome.

Bulbar and pseudobular palsy

These terms refer to impairment of function of muscles supplied by lower cranial nerves (IX X XI and sometimes XII). The nuclei of these nerves lie in the medulla (the medullary bulb), within the brainstem. Lesions involving the descending corticobulbar pathways (from cortex to nucleus) cause pseudobulbar palsy and lesions of the nuclei, fasciculi, cranial nerves or muscles themselves produce bulbar palsy. In pseudobulbar weakness, there is no lateralisation. Bulbar weakness can be unilateral, though it is typically bilateral. The most obvious manifestation of diminished muscle movement is usually choking and neurogenic dysphagia, but both bulbar and pseudobulbar palsy include a constellation of characteristic associated clinical features. Patients with severe Parkinson's disease also have poverty of movement of bulbar muscles, and cerebellar disease causes disordered swallowing.

Normal swallowing

The normal swallow is a complex sequence of coordinated events requiring intact lower cranial nerve function. A pre-oral phase is associated with the sight, smell and taste of food that triggers saliva production and prepares for the food or liquid bolus. In the oral phase the lips close to form a seal (VII); the tongue and rotatory action of the jaw (XII, V)) grind food, mixing it with saliva. The velum sits on the base of the tongue to seal off the nasal cavity. When the bolus has been formed the tongue raises against the hard palate, a central groove forms (XII) and the stripping motion of the tongue moves the bolus backwards. When the bolus reaches the faucial arches, the swallowing reflex is triggered. The pharyngeal stage is entirely involuntary. The soft palate rises to block off the nasal cavity (X). As the swallow is triggered the larynx rises and tilts forwards. The airway is protected by apposition of the true and false cords and of the arytenoids against the base of the epiglottis (the sphincteric action of the larynx). The epiglottis inhibits direct contact of the bolus with the laryngeal vestibule (all X). Upward and forward movement of the hyoid and larynx (V,VII, C1–3) enhance airway protection and pull open the relaxed upper oesophageal sphincter. The bolus moves over the closed airway and the cricopharyngeal sphincter relaxes. In the oesophageal stage the bolus passes through the cricopharyngeal oesophagus by peristalsis. Breathing is centrally inhibited during the swallow (deglutition apnoea); afterwards, structures return passively to their original positions, or with the aid of the infrahyoid muscles.

It is increasingly clear these swallowing reflexes are influenced by significant descending control to the medulla. Clinical observation in cerebrovascular disease and cortical mapping using transcranial magnetic stimulation and functional imaging indicate a role for the cerebral cortex (primary motor, inferior frontal gyrus and insula) with probable left hemispheric dominance. Dysphagia is also common in basal ganglia and cerebellar disorders – these systems are clearly also involved in descending control.

Bulbar palsy (Table 12.5)

While bulbar palsy may be unilateral or bilateral, swallowing impairment usually only occurs with bilateral weakness. Bulbar muscle weakness causes a nasal dysarthria, dysphagia with nasal regurgitation, a wasted atrophic tongue with fasciculation and slow tongue movement. There may also be associated facial weakness, dysphonia and limited jaw movement. There is consistent absence of both palatal and pharyngeal reflexes in bulbar palsy. Unilateral pharyngeal wall paresis causes the paralysed side to move towards the healthy side (Vernet's movement *de rideau*). It is not possible to distinguish reliably between IX and X nerve lesions, but lack of posterior pharyngeal sensation can have important implications in stroke. A unilateral XII nerve lesion causes tongue deviation – on retraction towards the healthy side (unopposed action of the styloglossus), and on protrusion towards the affected side (genioglossus). Impaired swallow can easily lead to poor dietary intake and dehydration, aspiration and bronchopneumonia – secretions pool in the pharynx.

Table 12.5 Causes of bulbar palsy.

Lesions of medullary cranial nerve nuclei	
Cerebrovascular	Infarction
	Haemorrhage
Tumour	Glioma
Infection	Poliomyelitis
Inflammatory	Multiple sclerosis
	Acute haemorrhagic leucoencephalitis
	Sarcoidosis
Degenerative	Motor neurone disease
	Kennedy's disease
Structural	Syringobulbia
Rhomboencephalitis	Bickerstaff's encephalitis†
	Fisher syndrome
Lesions of cranial nerves	
	Guillain–Barré syndrome
	Fisher syndrome
	CIDP
	CMT type II
Neuromuscular junction lesions	
	Myasthenia gravis
	Lambert–Eaton myasthenic syndrome
	Congenital myasthenia gravis
	Botulism
Muscle diseases	
Inflammatory	Polymyositis
	Inclusion body myositis
Dystrophy	Myotonic
	Duchenne
	Oculopharyngeal

CIDP, chronic idiopathic demyelinating polyradiculoneuropathy; CMT, Charcot-Marie-Tooth.

†Bickerstaff's encephalitis: rare, sometimes with anti-GQ1b antibodies, cranial nerve palsies, cerebellar ataxia, coma.

Pseudobulbar palsy (Table 12.6)

Pseudobulbar palsy describes an upper motor neurone pattern of weakness affecting muscles innervated by the bulbar nuclei. It is usually due to bilateral involvement of the descending corticobulbar and/or cortico-pontine pathways anywhere from the insular cortex to the medulla. Pseudobulbar palsy is characterised by spastic dysarthria, slow and limited tongue movements with no wasting or fasciculation, an exaggerated jaw jerk and pharyngeal weakness. There may be complete anarthria with an inability to open the mouth, protrude the tongue, swallow or move the face at will or on command. Patients with pseudobulbar palsy show a striking incongruity with loss of voluntary movements of muscles innervated by the motor nuclei of the lower pons and medulla (inability to swallow, phonate, articulate, move the tongue forcefully, close the eyes) but preservation of reflex ponto-medullary actions: yawning, coughing, throat clearing, spasmodic laughter and crying. Pseudobulbar affect decribes the combination of emotional lability and profound motor retardation. There may be associated frontal release signs and primitive reflexes; the jaw jerk, facial and pharyngeal reflexes can be particularly brisk, with clonic jaw movements or clamping down on a wooden tongue blade. Occasionally these clinical features occur in isolation with no other manifestations of pseudobulbar palsy. In particular, isolated inappropriate spasmodic laughing or crying, unrelated to surrounding circumstances or stimulation and with no corresponding emotional feeling may be the first feature sign of

Table 12.6 Causes of pseudobulbar palsy.

Cerebrovascular disease	Infarction
	Haemorrhage
	Vasculitis
Inflammatory	Multiple sclerosis
	Acute disseminated encephalomyelitis
	Acute haemorrhagic leucoencephalitis
	Sarcoidosis
Degenerative	Motor neurone disease – progressive bulbar palsy, amyotrophic lateral sclerosis or progressive lateral sclerosis
	Hereditary spastic paraplegia
	Progressive supranuclear palsy
	Corticobasal degeneration
	Multiple system atrophy
Inborn errors of metabolism	Friedreich's ataxia
	Mitochondrial disease
	Leigh's syndrome
	Adrenoleucodystrophy/adrenomyelodystrophy
	Alexander's disease
	GM2 gangliosidase deficiency
	Metachromatic leucodystrophy

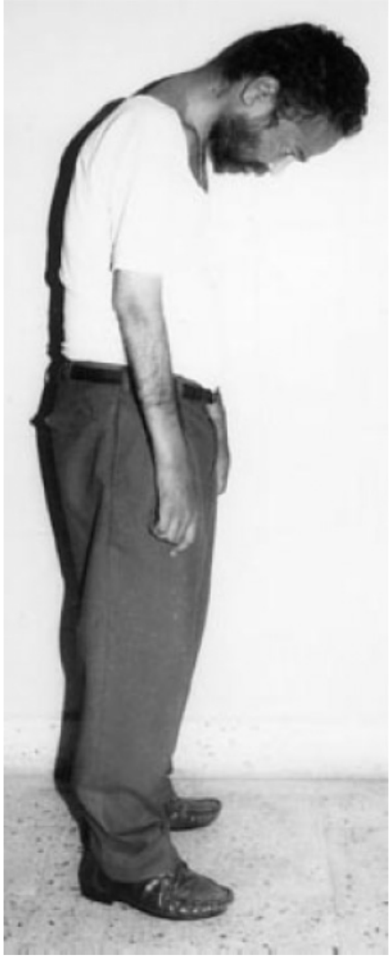

Figure 12.10 Dropped head syndrome in motor neurone disease. (From Gourie-Devi *et al.* 2003, with permission.)

pseudobulbar palsy. Movements of the palate and pharynx on phonation are variable but often reduced.

Pseudobulbar palsy may be divided into three forms;

1 Cortical – due to lesions in the opercular region and characterised by isolated weakness of the face, pharynx and tongue with dissociation between automatic and voluntary function. This is associated with anarthria, a complete loss of swallow and hypotonic paralysed muscles. Emotional lability is unusual.

2 Striatal – due to lesions in the descending corticobulbar tract in which the characteristic cortical features are associated with pyramidal signs, emotional lability and cognitive impairment;

3 Pontine – in which all these features occur with cerebellar signs and emotional lability but no cognitive impairment.

Dropped head syndrome

Certain clinical appearances narrow diagnostic possibilities. The dropped head syndrome (Figure 12.10) is one of these. A variety of neuromuscular diseases cause this syndrome (Table 12.7); motor neurone disease is one of the most common.

Table 12.7 Causes of dropped head syndrome. (From Gourie-Devi *et al.* 2003, with permission.)

Myogenic
Myasthenia gravis
Polymyositis
Isolated neck extensor myopathy
Facio-scapulo-humeral muscular dystrophy
Nemaline myopathy
Proximal myotonic myopathy
Inclusion body myositis
Carnitine deficiency
Adult onset acid maltase deficiency
Acute hypokalemic myopathy
Congenital myopathy
Focal myositis of extensor neck muscles
Neurogenic
Motor neurone disease
Spinal muscular atrophy
Chronic inflammatory demyelinating polyradiculoneuropathy
Miscellaneous
Hypothyroidism
Cervical dystonia
Local causes
Cervical spondylosis with neurogenic weakness of neck extensors
Ankylosing spondylitis

The condition is particularly distressing and difficult to help. Various supports and frames are sometimes suggested; in the authors' experience many patients find the most appropriate support, e.g. a high-backed chair or tailored U-shaped cushions. Advice from an occupational therapist with experience of palliative care is helpful. Severe neck pain often accompanies the weak muscles.

Multiple cranial neuropathies

Multiple cranial neuropathies (MCNs) are either caused by local lesions such as tumours, vascular causes, trauma and infection, which affect clusters of neighbouring nerves, or by underlying systemic conditions. Some combinations of cranial nerve lesions have been mentioned already; others are described in relevant chapters (e.g. Chapters 13, 14 and 20). Some MCNs have a benign cause, such as a CPA tumour. However, when no such lesion is evident on initial imaging, MCNs should be regarded as ominous, because of the high chance of underlying malignancy (metastasis, primary tumour and malignant meningitis) or other serious systemic disease. Careful scrutiny, a review of detailed imaging and CSF analysis are needed, and may need to be repeated after an interval. Images of the skull base are sometimes particularly difficult to interpret – fine-cut CT, with bone windows is in our experience of particular value. The advice and expertise of an ENT surgeon and an ophthalmologist with experience of neurological conditions is invaluable.

One large series of over 1000 cases of MCNs found that tumours were responsible for 30% (Tables 12.8 and 12.9). Schwannomas, generally from the VIIIth nerve, followed by metastases were the most common neoplasms. The majority of vascular cases were lateral pontine or medullary infarcts. Three arteriovenous malformations were found and eight carotico-cavernous aneurysms. Infection made up 10% of the series, with 48/102 neuropathies being caused by meningitis (22 bacterial, 9 tuberculous, 9 cryptococcal). Other causes included botulism (10), mucormycosis (8), viral encephalitis (8) and cysticercosis (6).

Table 12.8 Causes of multiple cranial neuropathies. (From Keane 2005, with permission.)

Cause*	Overall cases, No. (%)	Recurrent cases, No.
Tumour	305 (30)	2
Vascular disease	128 (12)	0
Trauma	128 (12)	1
Infection	102 (10)	1
Guillain–Barré syndrome	62 (6)	0
Fisher syndrome	29 (3)	0
Idiopathic cavernous sinusitis	56 (5)	10
Surgical complication	54 (5)	0
Multiple sclerosis and ADEM	54 (5)	0
Non-organic	26 (3)	0
Diabetes mellitus	25 (3)	14
Benign	23 (2)	14
Miscellaneous	22 (2)	0
Unknown	14 (1)	0
Total	1028*	43

ADEM, acute demyelinating encephalomyelitis.
* Some cases had more than one cause.

Table 12.9 Tumours causing multiple cranial neuropathies. (From Keane 2005, with permission.)

Tumour type	No. (%)
Schwannoma	53 (17)
Metastases	49 (16)
Meningioma	41 (13)
Lymphoma	29 (10)
Pontine glioma	28 (9)
Nasopharyngeal carcinoma	26 (9)
Pituitary adenoma	16 (5)
Chordoma	14 (5)
Leukaemia	8 (3)
Epidermoid	7 (2)
Glomus jugulare	6 (2)
Miscellaneous	21 (7)
Unknown	6 (2)
Total	305

Table 12.10 illustrates the localization of the pathology, with 25% affecting the cavernous sinus (particularly structural lesions and trauma) and 20% the brainstem (mainly vascular). Table 12.11 shows that the VIth nerve followed by the VIIth nerve were the most frequently involved, with common combinations (Table 12.12) being IIIrd + VIth, Vth + VIth and Vth + VIIth nerves.

Other causes of MCNs

Other causes of MCNs are sarcoidosis and vasculitides (Chapter 25). Nasopharyngeal carcinoma is an important cause of MCN; usually branches of the Vth nerve are involved initially, but with tumour spread the VIIth, VIth and lower cranial nerves may become affected. Cranial neuropathies are also discussed in Chapter 9.

Table 12.10 Location of cranial nerve damage. (From Keane 2005, with permission.)

Location*	No. (%)
Cavernous sinus	252 (25)
Brainstem	217 (21)
Nerve	182 (18)
Clivus and skull base	128 (13)
Subarachnoid space	101 (10)
Cerebellopontine angle	86 (8)
Presumed non-organic	26 (3)
Neck	21 (2)
Unknown	1 (0)
Total	1014*

*Some cases had more than one location.

Table 12.11 Cranial neuropathies: nerves involved. (From Keane 2005, with permission.)

Cranial nerve	Overall cases No.	Recurrent cases No.
II	155	1
III	339	36
IV	143	2
V	353	10
VI	565	26
VII	466	48
VIII	180	3
X	220	2
XI	48	0
XII	163	2
Total	2632	130
Mean involved/patient	2.7	3.0

Table 12.12 Common combinations of cranial lesions. (From Keane 2005, with permission)

Cranial nerve combination	Overall cases, No.	Bilateral cases, No.
III and VI	285	64
V and VI	214	11
V and VII	209	14
VII and VIII	135	2
III, IV and VI	126	30
V, VI and VII	125	7
II, III and VI	98	7
X and XII	89	17
V, VII and VIII	86	1
VI and XII	71	14
X, XI and XII	21	5

Multiple recurrent cranial neuropathy of unknown cause

A recurrent multiple cranial neuropathy of unknown cause is seen particularly in South-East Asia. Clusters of MCNs, such as IIIrd, Vth and VIIth nerve lesions, develop, remit and recur over several years. Some of these cases are responsive to steroids.

Intracranial epidural abscess

Pyogenic intracranial epidural abscess is a rare cause of progressive sequential multiple cranial nerve lesions on one side. This occurs typically in the elderly, and in diabetic and cachectic patients. For example, deafness with a discharge from the external auditory meatus can be followed by a VIIth nerve palsy and progressively by lower cranial nerve palsies, to include the XIIth. The abscess, a thin sheet of pus, little more than 1 mm in thickness, can also track upwards to involve the Vth nerve, the three oculomotor nerves and even the optic nerve, the process taking weeks or months. In the early stages, these abscesses can be hard to visualize on imaging. Surgical exploration is usually required, and high doses of antibiotics, but the condition carries a high mortality.

Acknowledgement

Professor MJT FitzGerald, Emeritus Professor, Department of Anatomy, University College, Galway and the publishers, kindly agreed that figures from the award-winning textbook *Clinical Neuroanatomy and Related Neuroscience* (FitzGerald MJT, Folan-Curran J, 4th edition, 2002; WB Saunders, Edinburgh) were made available for the authors to use in the preparation of this chapter; this has proved invaluable.

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13

Neuro-Ophthalmology

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Patients generally relate visual disorders to the eye itself rather than thinking that the problem might be with the brain. In the UK, when a patient complains that he/she has impaired vision the first port of call is frequently an optometrist and if spectacles are not the answer a further referral is made to a hospital through the general practitioner. In many other parts of the world without extensive service provision by optometrists and general practitioners the patient will see an ophthalmologist directly. A significant proportion of patients presenting with symptoms of visual abnormalities have primary neurological disorders or require neurological assessment. Therefore, ophthalmology and neurology should rightly be closely related disciplines, the eye is, after all, a part of the brain and many disorders of the brain have direct effects on vision.

Unilateral visual failure

History

Mode of onset. In taking a history from a patient complaining of visual loss in one eye it is first essential to establish whether the onset was acute, subacute or gradual and whether, since the patient noticed the problem, the vision has deteriorated, improved or remained static. It is best to establish exactly how and in what circumstances he/she first became aware of the problem because the patient may suddenly become aware of vision loss that has been coming on for some time. Some people do not seem habitually to close one eye unless having a specific reason to do so – such as acquiring a foreign body in one eye or during a visit to the optometrist. Thus, a reported abrupt onset of unilateral visual loss, in contrast to when both eyes are affected, may be spurious and the precise circumstances need to be reviewed with an appropriate degree of scepticism. Once it is clear that the loss of vision was genuinely abrupt, painless and with no subsequent change, a vascular cause (e.g. central retinal artery occlusion or anterior ischaemic optic neuropathy) is almost certain but it is important to remember that some vascular syndromes can cause progressive or fluctuating loss of vision.

Subacute loss over days, with pain, is in keeping with an inflammatory cause (e.g. optic neuritis) but the differential diagnosis remains wide unless there has been spontaneous recovery of vision because a number of compressive lesions are capable of producing the same syndrome: notably, anterior communicating artery aneurysm, infections or mucocoele of the paranasal sinuses. The consequences of misdiagnosing a compressive optic neuropathy such as optic neuritis can be disastrous as early intervention is required to prevent permanent visual loss. The general rule is that in demyelinating optic neuritis, associated with multiple sclerosis (MS), the pain precedes the loss of vision. Indeed, the pain often abates as the visual loss is noticed by the patient. Furthermore, the pain is not severe, rarely disturbing sleep and it may only be present on eye movement or even only on movement in a particular direction. Therefore an unusual degree of persistent pain would be one feature that should alert the clinician to a possible compressive cause or to an aetiology of optic neuritis requiring an entirely different approach to management such as a granulomatous or infective cause.

In many patients, the more typical history of gradually progressive loss of vision produced by a compressive lesion will be clear: in others, it may be necessary to acquire optometrist's records to confirm the tempo of the visual failure. Paradoxically, in some instances, loss of vision which would clearly have been abrupt at onset may not be noticed for some time – such as following a vascular occlusion that affected a part of the field only or following trauma. Again, any previous records of visual acuity or visual field testing will be invaluable. Another situation that causes confusion is when a patient is referred with asymptomatic unilateral visual field loss. Usually, visual acuity is normal in this situation and the patient presents with a visual field defect sparing central vision. It is first necessary to establish whether the patient had ever had a previous perimetric examination: if not the loss could

Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

be congenital. If it is clear that the loss has been acquired at some time between two examinations it may require some detective work to decide the cause based on the examination findings and on occasion serial perimetry to determine whether or not the defect is static. Unilateral visual field defects that present in this way are commonly caused by focal retinal pathology, congenital optic nerve defects, glaucoma, optic disc drusen, previous trauma, compressive lesions and chronic sequelae of subclinical branch retinal artery and vein occlusions and of demyelinating optic neuritis.

Positive symptoms. Positive symptoms are not commonly reported in optic nerve disease. Occasionally, patients with optic neuritis report that on eye movement a brief flash is perceived. Of interest, these flashes are not seen except in the dark, indicating that the perception is washed out by natural illumination. This is in contrast to positive stimuli generated in the occipital lobes which appear equally bright in the dark and in brightly lit surroundings. Patients who report continuous phosphenes (again appreciated more in low light levels) will have retinal disease and this is particularly true of cases of local retinitis such as the idiopathic big blind spot syndrome and acute zonal occult outer retinopathy. These two conditions are almost always unilateral and often referred as suspected optic nerve disease because the retina appears normal on fundus examination but there are discrete scotomas typical of retinal disease and within which the patient is aware of a more or less constant flickering.

Effect of light level. Humans have a duplex retina in which two independent systems of photoreceptors – the rods and cones – are specialized for low and high light levels, respectively. Indeed, in extreme low light levels the cone photoreceptors make no contribution to vision and at photopic levels the rods do not function. Hence, conditions that affect more or less independently the two classes of photoreceptor result in visual loss that is much more marked at low light levels (nyctalopia, e.g. rod dystrophies) or at high light levels (e.g. cone dystrophies); these disorders are rarely unilateral. However, post receptorally the rod and cone signals are shared (multiplexed) by the same pathways (bipolar cells and retinal ganglion cells). Hence, in optic nerve disease marked variation in visual performance at different light levels is not generally observed. There are exceptions to this and some patients with optic neuropathy may report seeing better in bright or dim light although it may be difficult to understand why. A more specific situation which occurs in demyelinating optic neuropathy is deterioration in bright light which patients describe as ‘fading’. The pathophysiological basis of this is not known.

Direct questions. The following are a few direct questions worthwhile asking any patient with unilateral visual loss.

- *Subjective visual field changes* ‘If you are viewing with that eye alone, is the entire field of vision affected, or only a part?’ Central scotomas are frequently reported as appearing as if there is a cloud or other patch in front of the eye, saying: ‘If only I could see around it my eyesight would be normal.’ Patients with altitudinal field defects may have normal visual acuity but be aware that they cannot see above or below what they are looking at and this is highly suggestive of either anterior ischaemic optic neuropathy or a branch retinal artery occlusion.
- *Provoking factors* ‘Does vision deteriorate after exertion or a hot bath?’ In Uhthoff’s symptom vision deteriorates with a rise in body temperature, returning to normal when the body cools down. This phenomenon is almost pathognomonic of demyelinating (MS-associated) optic neuritis. The loss of vision may be total or partial but recovery always occurs after a few minutes of resting. Most commonly, the symptom is noticed by patients who have recovered from acute optic neuritis but it may also occur in the acute phase or in patients who do not report an acute episode at all, that is to say as a result of subclinical demyelination.
- *Associated symptoms* ‘Have you noticed any change in your sense of smell?’ In cases of anterior cranial fossa masses (usually meningiomas) anosmia may precede loss of vision by several years and may well have passed without any neuroimaging being carried out.
- *Double vision* ‘Have you had double vision?’ The ocular motor nerves enter the orbit through the superior orbital fissure while the optic nerve enters through the optic canal and the combination of an optic neuropathy with a IIIrd, IVth or VIth cranial nerve lesion would indicate either an extensive lesion (and this can occur with meningiomas and granulomas) or the pathology must be within the orbit itself and on examination the neurologist should look particularly for orbital signs.
- *Distortion* ‘Do you see distortion of anything that you are looking at, do straight lines appear crooked or do objects appear larger of smaller than they should?’ Rarely, spatial distortion of images can occur with occipital lobe disease. This does not occur with optic nerve disease but is very commonly seen with retinal disease. A distorted photoreceptor layer will result in an equivalent geometric distortion of the perceived image. Thus, elevation of the retina will result in separation of the photoreceptors and the perceived image will be diminished in size and any other distortion of the photoreceptor layer will lead to a predictable distortion of the image. Central serous retinopathy in younger patients or age-related macular degeneration in older patients are the disorders that are most commonly confused with optic nerve disease and this simple question can provide an important clue.

Examination

Visual acuity. The first step for the neurologist is to decide whether unilateral visual loss is caused by refractive error, disorders of the lens and ocular media or retinal pathology and hence would require onward referral for appropriate management. Some knowledge of optometry is essential because the presence of emmetropia, myopia or hypermetropia and presbyopia has a marked effect on how patients respond to changes in vision resulting from neurological disease and also on the interpretation of findings on examination including the appearance of the fundus. Visual acuity examination is a highly technical affair that requires carefully calibrated charts and standardized conditions of illumination. Outside optometry and ophthalmology clinics a grubby and faded acuity chart hanging on the back of a door or even worse a magazine borrowed from the waiting area may be all that is available: the importance of an accurate and repeatable assessment of visual acuity cannot be overemphasized. We need to know the distance and near acuity, with and without the patient's own correction if worn and then again with pin-hole correction.

Colour vision. The testing of colour vision can be performed simply by asking the patient to judge the saturation of a coloured target. 'Saturation' in chromatic terms refers to how close the colour is to white and it is generally the case in optic nerve disease that colours will appear less saturated – that is to say, closer to white. Quite simply, in unilateral optic nerve disease if a coloured target is held up to the affected eye and a comparison made with the unaffected eye this difference in colour will be reported. At the extreme the colour may be lost all together and the object will appear white or grey depending upon its luminance brightness. Tests are available in which patients are shown a series of chips of the same hue varying in saturation and are asked to arrange them in order of increasing saturation which will indicate the least saturated chip that is perceived as being different from white. The degree of saturation can be quantified in this way.

Across the visual field this change can be observed regionally so that in a patient with a central scotoma which is relative the colour saturation of the target may be restored as it is moved from an abnormal to an unaffected region of the visual field. This is of particular importance when a hemianopic or altitudinal field defect is suspected as this change in colour saturation will appear abruptly as the target is moved across the vertical or horizontal meridian, respectively.

The Ishihara pseudoisochromatic plates are commonly utilized for the assessment of colour vision in ophthalmic and neurological practice. The term 'pseudoisochromatic' refers to the fact that the individual coloured dots which make up the figure are varied in brightness, thus making it impossible to use luminance differences to identify the figure. The advantage of this in the assessment of unilateral visual loss is that impairment of colour vision in optic nerve disease is much greater (for an equivalent loss of acuity) than in the case of retinal disease. The explanation for this is not known but it may in part be related to a selective effect of compressive and demyelinating optic pathology on the parvocellular pathway (these are the retinal ganglion cell axons that project to the parvocellular layers of the lateral geniculate nucleus and which subserve colour vision). In retinal disease the extent to which colour vision is affected can be predicted from the degree of involvement of the macular and paramacular regions of the retina. In other words, if acuity is reduced and there is a large enough central scotoma then colour vision will be affected. At the limit, patients with visual acuity of 6/60 cannot read even the control plate in the Ishihara test. This plate does not require any colour vision to read but indicates that the patient has adequate visual acuity to perform the test. In optic nerve disease, a patient with a visual acuity of 6/6 or 6/9 is likely to have significantly impaired colour vision and this would be very unusual in retinal disorders with the exception of the cone dystrophies. At a conventional viewing distance the Ishihara plates subtend 15–20 degrees of visual angle while foveal visual acuity depends upon the integrity of the central one degree of the visual field only. Thus, a paradoxical result mimicking optic nerve disease – relatively preserved central acuity with impaired colour vision – may occur in a patient with a maculopathy resulting from retinal disease but with sparing of a tiny central island.

The Ishihara plates were developed for the assessment of congenital colour anomalies (Daltonism) and so there is considerable detail in the testing that is not relevant to optic nerve disease where the losses do not follow the specific patterns seen in Daltonism but show largely global losses. Furthermore, specific illumination conditions are required for an accurate interpretation of errors. Therefore, loss of colour vision can be broadly quantified by recording the number of errors made on the charts but there is little to be gained from recording the individual errors. An exception to this is if the patient misses all of the numbers on the left or right-hand side of the double figure numbers as this may indicate a hemianopic defect on that side in that eye. It is also worth observing the speed with which the patient is able to read the numbers. This should be instantaneous and any reduction in the speed of reading in one eye is certainly significant. Some appreciation of the effect of Daltonism on performance on these plates is necessary so that results can be interpreted in the patients (mostly males) who are so affected.

Amsler's test. The Amsler grid is a very useful tool as patients may be able to visualize scotomas or report distortion (see above). The findings can be recorded and used for serial monitoring of any defect. In fact, it is common practice to use the recording sheet (a black grid on a white background) for testing as well as recording rather than the test plates which are considerably more sensitive being a white or red grid on a black background.

Visual field testing. Confrontation perimetry remains an essential skill. A rapid assessment of the visual field can be obtained in any situation and any clinical environment. Monitoring of fixation is straightforward (even if the patient's cooperation may be problematic) because the patient is asked to fix on the tester's eye. In the case of unilateral visual loss not only should the visual loss in the affected eye be plotted but the other eye should be tested carefully for any evidence of a contralateral temporal hemianopic visual field defect as this immediately gives the location of the lesion as involving the prechiasmal portion of the optic nerve and the chiasm itself. Such defects are best demonstrated looking for colour desaturation. There is considerable discussion in the literature regarding junctional visual field defects (i.e. defects affecting the junction of the optic nerve and chiasm) and most readers will have heard of the 'junctional scotoma' and 'Wilbrand's knee' of optic nerve fibres which loop forward into the contralateral nerve before crossing in the chiasm. Suffice to say that the junctional scotoma (first described by Traquair) is a temporal hemianopic scotoma found in an eye that shows signs of optic neuropathy: an upper temporal hemianopic defect in the fellow eye was described by Wilbrand. Whatever the anatomical explanation of these phenomena, the essential practical point is that a temporal hemianopic defect in either eye of a patient with unilateral visual loss immediately places the problem to the chiasm.

It is beyond the scope of this chapter to give detailed descriptions of other perimetric techniques such as Goldmann and Humphrey automated perimetry but these methodologies must be familiar and their respective advantages and disadvantages must be appreciated. In a patient with unilateral visual loss either method can be used but in certain respects the information provided is complementary. The Goldmann perimeter uses kinetic testing – the target is moved from an area where it is invisible to a seeing area and the patient is asked to report when he/she sees it, usually from the periphery towards the centre in plotting isopters (lines of equal sensitivity) for any particular size and brightness of target: thus, a scotoma can be plotted (including the physiological blind spot) by moving the target from within the scotoma to its borders.

The Goldmann perimeter can also be used for static testing. The target spot is flashed on at a particular location in the visual field and the patient asked whether or not it was detected. The brightness of the target can then be adjusted to determine the *threshold* – the smallest increment of the target over the background that the subject can detect. To cover the entire visual field in this way can be extremely arduous and the method of plotting isopters to kinetic targets remains the most efficient way of screening the visual field; however, some static points should be tested within the central field to look for any evidence of central or paracentral scotomas.

The Humphrey and Octopus automated perimeters are in use in most ophthalmology departments and at the time of writing the manually operated Goldmann perimeter is no longer being manufactured. The automated perimeters are based on the Goldmann in that the target size employed is the same as one of the standard settings on the Goldmann (size III) and indeed the field plot produced for the Humphrey perimeter is the same scale as the Goldmann charts (they can be overlapped and held up to the light to compare them). The test is automated and the operator merely stands by to monitor fixation, encourage the patient and so on. The most commonly used plot that the reader will come across is limited to the central 30 degrees of the field and threshold sensitivity is measured along a grid of points covering the area. These automated machines are being modified to permit the kind of kinetic testing that is carried out on the Goldmann but this will be more time-consuming and lack the specific strategies that can be employed by the experienced Goldmann operator.

Interpretation of visual fields requires considerable knowledge. An understanding is required of refraction and it is necessary to be familiar with a whole host of potential artefacts and what happens when the subject is fatigued, etc. For the neurologist non-specialist the most useful skill is to be able to carry out competent confrontation fields but for a detailed consideration of complex cases and strategies for monitoring it will be necessary to turn to colleagues with neuro-ophthalmic expertise.

The pupil light reflex

The examination of the pupil light reflex is of fundamental importance in the assessment of unilateral visual loss. If one eye is blind (from whatever cause) and the other sees then there will be no direct pupil light reflex when the blind eye is stimulated although the consensual will be intact – an afferent pupillary defect. Indeed, if there is a pupil light reflex then the eye cannot be genuinely blind and a non-organic cause for the visual loss is confirmed. In this situation care must be taken not to allow stray light to fall in the seeing eye as this will give rise to a spurious response in the blind eye. However, the variance of the amplitude of the pupil light reflex in the population is so great that even under laboratory conditions, where the background luminance and the luminance of the stimulus are carefully controlled only at the extremes such as a blind or near-blind eye, can an abnormal response amplitude be reliably discriminated from a normal response. So what hope is there for a neurologist in a variably lit out-patient clinic and a flickering pen torch with a dying battery? However, in the case of unilateral partial visual loss the strength of the pupil light reflex in the two eyes can be compared. This can be done by either covering each eye in turn or by shining a light in each eye in turn: this latter strategy has become known as the ‘swinging flashlight test’ and is most commonly employed. The test makes use of the slow response time of the pupil light reflex (200 ms). The light source can be ‘swung’ from one eye to the other and back again without the pupils returning to the size determined by the background light level in the room. In a case of unilateral partial visual loss, if we look at each pupil light reflex in isolation we obtain a response which will look much the same but we can demonstrate a *relative* afferent pupillary defect because when the light source stimulates the affected eye (or more affected eye in the case of bilateral asymmetric loss) it will be as if the light source is dimmer, so both pupils will dilate, constricting again as we return to the unaffected eye. The test is used to confirm damage to the retina or optic nerve (in refractive error, lens opacity and amblyopia the pupil light reflex will not be affected) but it is much more sensitive in optic nerve disease. Retinal dysfunction must be extensive before the pupil light reflex is affected whereas in relatively mild optic nerve disease it will be possible to demonstrate a relative afferent pupillary defect. The test is especially useful in the detection of optic neuritis and compressive optic neuropathy where eyes with near-normal acuity may be shown to have a relative afferent papillary defect but eyes with 6/60 visual acuity can be shown unequivocally not to have optic nerve disease because the pupil light reflex is normal.

Fundus examination. The primary interest is in the appearance of the optic disc and there are some important rules. The emphasis traditionally has been on the observation of a pale optic disc as evidence for optic neuropathy – but there is considerably more detailed information to be obtained. First, it is important to observe the morphology of the optic disc and in particular the size of the cup. In the management of glaucoma the degree of cupping of the optic disc is of fundamental importance and it is essential to know the difference between normal cupping, pathological cupping in optic nerve disease and pathological cupping specific to glaucoma. In hypermetropia there tends to be a small cup or none at all (crowded optic disc) while in myopia the disc can be very large so it is necessary to be familiar with identifying the neural elements within the disc circumference which is defined by the scleral opening.

Furthermore, we are interested not only in pallor of the disc but more directly with loss of the optic nerve fibres which is the primary pathology leading to the development of atrophy. The retinal nerve fibre layer is the closest layer to us as we examine the retina with the ophthalmoscope. The vessels, the arterioles and venules of the retina itself are in this same layer and it is the retinal nerve fibres (the retinal ganglion cell axons) that fill in the space between the vessels, altering in a subtle way the optical properties of the retinal surface. With some practice it is possible to observe thinning of this layer and the disappearance of sectors and slits associated with focal pathology at the disc.

Once familiar with the variations in morphology of the disc in health and disease and the changes that occur in the optic nerve fibre layer we can be confident in ascribing loss of vision to disc-related pathology (e.g. glaucoma, optic disc drusen, papilloedema) or to retrobulbar disease (optic neuritis or compressive optic neuropathy). It must be remembered also that severe retinal disease (especially retinal dystrophies) can lead to loss of retinal ganglion cells and thence to the appearance of optic atrophy. Another important fact is that it takes 4 – 6 weeks for the loss of retinal nerve fibres and optic atrophy to appear following an acute insult to the optic nerve. If a patient presents with a history of visual loss of less than a month but optic atrophy is already visible then the pathological process must predate the first symptom. This indicates that either the patient noticed the loss of vision sometime after the onset (as occurs in compressive optic neuropathy) or that there has been a previous subclinical event (as might occur in MS).

Swelling of the optic disc occurs in a number of pathological situations such as acute optic neuritis, acute ischaemia, retinal vein occlusion and in raised intracranial pressure. The disc may also be swollen chronically in the case of a hypermetropic crowded disc or in the presence of buried drusen.

The vessels are also of interest, not only in primarily vascular disease but also in compressive optic neuropathies because of the development of retinochoroidal collaterals (previously, and erroneously, known as optico-ciliary shunt vessels). In order to understand this phenomenon it is necessary to understand that there are two possible routes for venous blood to leave the eye: the ophthalmic vein, which is the continuation of the central retinal vein, and thence to the cavernous sinus and the choroidal veins which drain into the vortex veins and thence to the external jugular system. Any pathology that gives rise to retinal venous hypertension will tend to lead to the opening up of collaterals between the retinal branch veins and the choroidal veins. Occlusion of the central retinal vein is a common cause of this but any pathology that compresses the ophthalmic vein – typically, optic nerve sheath meningioma – will result in the formation of these collaterals. Papilloedema is another cause because the ophthalmic vein has a short course in the subarachnoid space and a rise in pressure in intracranial pressure will lead to retinal venous hypertension.

In inflammatory disorders of the optic nerve, such as MS and sarcoidosis, there may be evidence of periphlebitis or vitritis but these changes are more marked in sarcoidosis than in MS.

The macula is inspected primarily to look for any evidence of a maculopathy that could mimic optic nerve disease such as central serous retinopathy or a cone dystrophy. However, exudates around the macula (a 'macular star') are seen in neuroretinitis. The clinical features resemble optic neuritis but the inflammation must be very anterior, possibly involving the ganglion cell layer, for sufficient retinal oedema to be generated for the macular star to result.

Associated features

Thorough general, ophthalmological and neurological examinations must be undertaken but specifically signs of orbital disease should be sought, such as proptosis or motility defects; sense of smell must be tested; evidence of sinus disease sought as well as any clues to pre-existing CNS dysfunction caused by MS.

The causes of transient unilateral visual loss are summarized in Table 13.1 and those of sudden unilateral visual loss in Table 13.2.

Table 13.1 Causes of transient monocular blindness.

Vascular[1]	Central retinal artery emboli (transient monocular visual loss)
	Retinal or choroidal ischaemia
	Partial retinal vein occlusion
	Carotid artery stenosis or occlusion (e.g. atherosclerotic plaque, thromboembolism, dissection, radiation damage)
Migraine	Uncertain whether monocular visual loss occurs in migraine
Hypoperfusion	Hypotension, hyperviscocity, hypercoagulability, carotid disease, giant cell arteritis
Ocular	Intermittent angle closure glaucoma
	Retinal detachment
Vasculitis	Giant cell arteritis
Others	Inflammatory – Uhthoff's phenomenon
	Idiopathic
	Psychogenic
Obscurations[2]	Papilloedema due to raised intracranial hypertension causes transient visual obscurations
	Optic nerve tumours (e.g. gaze-evoked amaurosis in optic sheath meningioma)

[1] Duration of several minutes.

[2] Duration of seconds only.

Table 13.2 Sudden-onset monocular visual loss.

Vascular	Non-arteritic anterior ischaemic optic neuropathy (posterior ischaemic optic neuropathy is rare) Arteritic anterior and posterior ischaemic optic neuropathy Branch or central retinal artery occlusion Branch or central retinal vein occlusion
Inflammatory	Systemic inflammatory diease (rare)
Traumatic optic neuropathy	
Retinal detachment	
Vitreous haemorrhage	
Functional visual loss	

Bilateral visual failure

The diagnostic problem of progressive bilateral visual loss is usually soluble with a clear understanding of the knowledge of the visual pathways, patterns of visual symptoms and careful examination. Visual loss in both eyes may develop over months, weeks or days.

1 If visual loss >6/9 develops on a background of previously normal visual acuity, this should be investigated, initially by an optometrist and/or an ophthalmologist and, if visual loss remains unexplained, by a neurologist.

2 Progression of visual loss or progressive visual symptoms should always be investigated.

3 Accurate measurement and recording of visual acuity is essential. A 2- or 3-m hand-held Snellen chart is useful, even though these are less accurate than the standard 6-m wall chart. A pin-hole (this corrects up to 4 dioptres of refractive error) is essential.

4 As with uniocular visual loss, substantial diminished vision is sometimes an almost incidental finding in the context of vague visual complaints.

The principal issue is to distinguish between ocular disease and disease of the neural pathway:

- Refractive errors, cataracts, uveitis, macular degeneration, bilateral retinal disease;
- Optic nerve disease;
- Conditions affecting the optic chiasm, and beyond, to the cortex.

Post-chiasmal conditions, such as optic tract lesions, are relatively rare. Others, such as optic radiation lesions, visual association area and bilateral occipital lobe infarction, tend to present acutely. Bilateral visual loss, with progression, that does not have an organic basis is relatively common. Its features are characteristic and need to be recognized. Non-organic visual impairment must be distinguished from cortical visual loss.

For the general neurologist, matters can be compounded by unfamiliarity with the fine detail of ophthalmology and the relative inexperience of ocular and retinal conditions. Conversely, for the ophthalmologist, chiasmal compression will be less familiar than the patterns of common ocular disease; also, specialized brain imaging may not be readily available.

Table 13.3 Sudden-onset fixed bilateral visual loss.

Occipital lobe infarction
  Acute basilar artery occlusive disease
  Posterior circulation hypoperfusion (posterior watershed infarction)
  Sagittal sinus thrombosis
Pituitary apoplexy
Posterior reversible encephalopathy syndrome
Toxic encephalopathy (due to drugs, e.g. ciclosporin, methotrexate, vincristine)
Head trauma
Functional visual loss

The causes of progressive bilateral visual loss include the following:

1 *Ocular and retinal conditions*
Refractive errors and cataracts
Macular degeneration
Uveomeningitic syndromes
Retinal disease:
  Diabetes
  Neurodegenerative conditions
  Paraneoplastic degenerations
2 *Bilateral optic nerve disease*
Leber's hereditary optic neuropathy
Other bilateral optic nerve lesions
Papilloedema as a cause of visual failure
Toxins, drugs and radiation
3 *Chiasmal disease*
Chiasmal compression by mass lesions
Chiasmal compression by meningitic conditions
Chiasmal (and optic nerve) glioma and meningioma
4 *Post-chiasmal disease*
Optic tract and radiation lesions
Visual association area lesions
Cortical visual loss
5 *Non-organic visual failure*

The causes of sudden onset fixed bilateral visual loss are summarized in Table 13.3 and progressive visual loss in Table 13.4.

Optic nerve disease

Optic neuropathy

Optic nerve lesions generally lead to monocular visual loss and pain is a frequent accompanying features. The causes of optic nerve disease are listed in Table 13.5.

Inflammatory optic neuropathies (optic neuritis)

Nosology of optic neuritis. Terminology is clearly of importance but there are some difficulties (Table 13.6). If we refer to all cases of subacute visual loss with an inflammatory cause as 'optic neuritis' (which tends to be the current practice) it frequently happens that cases that are not associated with MS (see below) are managed inappropriately. However, if we use the term 'MS-associated optic neuritis' this is inappropriate for patients presenting with clinically isolated syndromes because of the need to await evidence of dissemination in time and space (whether judged clinically or on imaging) before a diagnosis of MS is made. Demyelinating optic neuritis is an alternative. However, there are certainly some cases of optic neuritis that behave exactly like a demyelinating episode, as occurs in MS, but the disorder is either a monophasic illness or even if recurrent there is never any evidence for MS clinically, on imaging or cerebrospinal fluid (CSF) studies. Nonetheless, the term 'demyelinating optic neuritis (DON)' is used on the understanding that a likely association with MS is implied and that the term MS-associated optic neuritis (MS-AON) is employed once the diagnosis of MS is secure.

Table 13.4 Neurological causes of bilateral progressive visual loss.

Anterior visual pathway inflammation	Optic neuritis Sarcoidosis Meningitis
Anterior visual pathway compression	Tumours Aneurysm Dysthyroid
Hereditary optic neuropathy	Leber
Optic nerve drusen	
Low tension glaucoma	
Papilloedema	
Toxic and nutritional optic neuropathy	
Drugs	
Radiation damage	
Paraneoplastic retinopathy	

Table 13.5 Causes of optic neuropathy.

Inflammatory	(See Table 13.6)
Ischaemic	Arteritic ischaemic optic neuropathy Non-arteritic anterior and posterior ischaemic optic neuropathy
Infections	(See Table 13.6)
Congenital/genetic	Optic disc anomalies/dysplasia – hypoplasia, coloboma, tilted disc, excavation Leber's herditary optic atrophy Autosomal dominant optic atrophy
Compressive/infiltration	Optic tumours Glioma Meningioma Metastases Lymphoma, leukaemia Abscess Carotid/ophthalmic artery aneurysm Thyroid ophthalmopathy Orbital pseudotumour Idiopathic intracranial hypertension
Toxic – drugs	Toxins Nutritional deficiency (B_1, B_{12}, folate) Tobacco Alcohol Radiation
Trauma	
Neurodegenerative disorders	Leucodystrophy Storage disorders – mucopolysaccharidosis, sphingolipidosis, perioxisomal disorders Hereditary ataxia Hereditary motor sensory neuropathy

Table 13.6 Causes of optic neuritis.

Demyelinating	Idiopathic Multiple sclerosis Acute disseminated encephalomyelitis Devic's syndrome	
Infectious	Bacterial	Borrelia, syphilis, mycoplasma, tuberculosis, Whipple's disease
	Viral	Herpes simplex zoster, EBV, CMV, Coxsackie, hepatitis A & B, measles, mumps, rubella
	Parasitic	Toxoplasmosis, cysticercosis, *Toxocara*
	Fungal	*Cryptococcus*, *Aspergillus*, mucormycosis, *Candida*
Post-vaccination		
Other inflammatory disorders	Sarcoidosis Connective tissue disorders (Sjögren's syndrome, systemic lupus erythematosus) Vasculitis (including polyarteritis nodosa, Wegener's granulomatosis)	

CMV, cytomegalovirus; EBV, Epstein–Barr virus.

Association with multiple sclerosis (demyelinating optic neuritis)

Clinical features

Unilateral optic neuritis is one of the most common causes of subacute unilateral visual loss. It is first essential to distinguish optic neuritis associated with MS from other causes. In Caucasian populations in temperate latitudes MS will be the most common form of optic neuritis seen but in other parts of the world and in non-Caucasian populations this will not be the case.

Almost all patients experience pain on eye movement prior to noticing loss of vision but this is rarely severe and as a general rule will not interfere with sleep. Severe or persistent pain should lead to a consideration of other disorders such as a granulomatous optic neuropathy or a sinus mucocoele. If the nerve is affected entirely intracranially there will be no pain but this occurs in only 10% of cases. Loss of vision progresses over a matter of days and can be minimal (indeed may not be noticed by the patient) or lead to no light perception. Colour vision and the pupil light reflex are impaired disproportionately to the acuity loss. Central visual field defects are typical but not found universally (Plate 13.1). There is always a degree of spontaneous recovery and 95% of cases will recover to a visual acuity of 6/9 or better.

Investigations

In patients where the clinical context and symptomatology point to a diagnosis of MS-associated optic neuritis, in most instances the diagnosis can be made on clinical grounds. However, there may be uncertainty and the investigations should follow the protocol given below for ‘atypical’ forms of optic neuritis. It is customary to check erythrocyte sedimentation rate (ESR), a chest X-ray and syphilis serology. Magnetic resonance imaging (MRI) of the optic nerves will almost always show high signal in the affected optic nerve on T2 weighted (or STIR) orbital images (Fig. 13.1) with gadolinium enhancement but, as already stated, this is not often necessary to make the diagnosis.

However, the other issue is whether imaging of the brain and spinal cord shows evidence of MS. A completely normal MRI of the brain makes it relatively unlikely that the patient will go on to develop further episodes. Most of the published studies are limited by the length of the period of follow-up as it is well established that some patients with optic neuritis have no further symptoms for some time – even 10 or 15 years – before a second, MS defining, clinical episode occurs. However, recent studies of unilateral optic neuritis as a clinically isolated syndrome report figures of around 50% of clinically definite MS after very long periods of follow-up (15–20 years). The risks are different for cases of bilateral simultaneous optic neuritis and for chiasmitis (see below).

Treatment

Many studies have now confirmed that the use of corticosteroids in acute MS-associated optic neuritis reduces the time taken for the vision to recover but does not alter the eventual outcome. This means that around 5% of patients will be left with poor vision in that eye and there seems to be no way of influencing this.

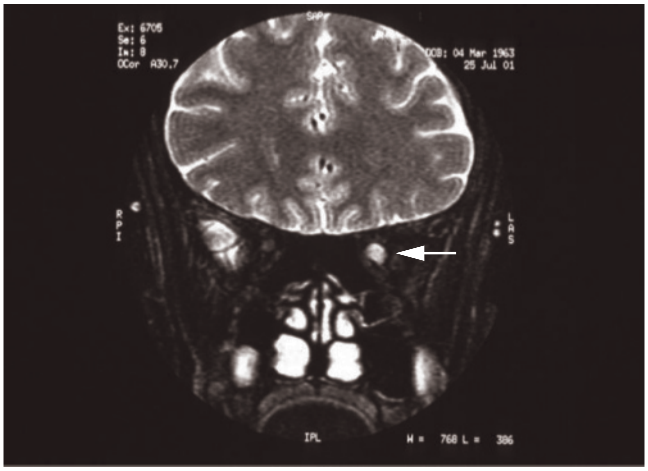

Figure 13.1 Acute optic neuritis. High signal from a swollen left optic nerve (MRI T2W fat supression).

Optic neuritis associated with neuromyelitis optica (Devic’s syndrome)

Clinical features (Chapters 10 & 15)

The optic neuritis seen in neuromyelitis optica (NMO; Devic’s syndrome) may result in very severe loss of vision – including permanent total loss of vision which is never seen in MS-AON. It is essential to consider the possibility of NMO as the underlying cause in any case of isolated optic neuritis and particularly if there is a previous history of myelitis. The full clinical spectrum of the phenotype is becoming clearer and the prognosis is normally worse than in MS-AON although not universally so. NMO is an autoimmune disorder and hence is associated with other autoimmune conditions and the diagnosis should be considered in any patient with previous evidence of an autoimmune phenotype. The disorder is more common in those parts of the world where MS is less often the cause of optic neuritis and it seems to be very closely related to the ‘Asian optico-spinal form of multiple sclerosis’. Therefore, the patient who grew up in latitudes where MS is less likely is considered particularly at risk of having NMO.

Investigations

The NMO-antibody (anti-aquaporin-4 antibody) should be sought in any case of atypical optic neuritis. It is not clear whether there are any specific features on optic nerve imaging as is the case with the spinal cord lesions (Chapter 15).

Treatment

The majority of patients who have had both optic neuritis and the typical spinal cord lesions of NMO will be found to have

NMO (anti-aquaporin 4) antibodies. There is also a small subgroup of patients who have recurrent optic neuritis alone without myelitis and who have the same antibody, about 5–10% of cases of optic neuritis for whom no specific cause (including MS) can be identified. However, the diagnosis is an important one to make because the management of NMO is quite different from the management of MS. Long-term immunosuppression is effective in preventing relapses and plasma exchange may be used in acute episodes (Chapter 10).

Optic neuritis: chronic relapsing inflammatory optic neuropathy

Clinical features

Chronic relapsing inflammatory optic neuropathy (CRION) is a condition that is not yet clearly defined and has an unknown aetiology. Presentation is with painful subacute visual loss but the pain is frequently more severe and prolonged than in MS-AON. In most cases the second eye is involved but not simultaneously. However, the essential point is that there is not only a response to corticosteroids but a relapse when these are withdrawn. This is entirely different from MS-AON where it is possible to give very short courses of high-dose steroids (even as short as 3 days) without fear of relapse when the course is completed. However, relapse is also common in optic neuropathy in neurosarcoidosis and it can be the case in optic neuritis associated with NMO antibodies. Another feature often seen in CRION is late improvement (i.e. a long-standing optic neuropathy which appeared static can show recovery with corticosteroid therapy).

Investigations

By definition, investigations are normal. Any evidence for an underlying systemic condition such as a vasculitis or granulomatous disorder must be excluded. There is no evidence of MS or NMO on imaging nor on CSF examination. A small number of patients with this phenotype do appear to have NMO antibodies.

Treatment

The response to immunosuppression suggests that the essential difference between CRION and MS-AON is that in the former there is ongoing inflammation whereas in MS there is a brief period of inflammation of acute onset which then subsides moving to a recovery phase. CRION is therefore appropriately treated with long-term immunosuppression and steroid-sparing agents. It is important to bear in mind that relapse can be associated with irreversible visual loss unless treated promptly.

Optic neuritis: infectious disorders

Clinical features

It is important to recognize these causes of optic neuritis because they require immediate and aggressive management. Viral infections can give rise to optic neuritis either by direct infection of the optic nerve or as a post-infectious syndrome. Bacterial infection of the optic nerve or sheath, such as in pneumococcal meningitis, can result in devastating visual loss as can fungal invasion (e.g. with *Aspergillus fumigatus*). Optic neuritis is one of many possible ophthalmic complications of neurosyphilis (Plate 13.2) and of another spirochetal disease, Bannwart syndrome (Lyme disease), caused by *Borrelia bugdorferi*. In most cases there will be some clear evidence of the causative infective process for instance herpes zoster ophthalmicus, or bacterial meningitis. It is most important to be vigilant in any case at risk of an underlying infection such as syphilis, tuberculosis, sinus disease or fungal infection. Atypical features of optic neuritis such as orbital signs or prolonged and severe pain should alert the physician to the diagnosis. In many of these infective cases the optic nerve sheath is involved rather than the optic nerve itself and the presenting syndrome is one of optic perineuritis (see below).

Investigations

Serological testing for syphilis should be undertaken in every case of optic neuritis presenting as an isolated syndrome. Other serological tests will defend the clinical presentation. Tuberculin testing may be required as may lumbar puncture, sinus biopsy and, occasionally, optic nerve biopsy. MRI of the optic nerve may give important clues in that the appearance may be of optic perineuritis rather than of swelling and inflammation affecting the intrinsic optic nerve and there may be evidence of infection elsewhere in the orbit, the paranasal sinuses or intracranially.

Treatment

The management of these disorders is discussed in Chapter 8.

Optic neuritis: sarcoidosis-associated optic neuropathy

Clinical features

In neurosarcoidosis, optic neuropathy is not uncommon. Some patients have a syndrome indistinguishable from MS-AON with spontaneous recovery but more commonly the optic nerve is infiltrated with granuloma. This process may be visible at the optic disc and there is much greater likelihood of a vitritis and of periphlebitis than in MS-AON. The optic nerve may also be compressed extrinsically by a granulomatous mass and because of this another common feature is the contiguous involvement of nearby structures, such as diabetes insipidus arising in sarcoid chiasmitis and associated orbital signs (Fig. 13.2). Sarcoidosis is also a cause of optic perineuritis (see below).

Investigations

When there is intrinsic optic nerve disease the optic nerve on imaging is more likely to be enlarged than in MS-AON. There may be a granulomatous mass and features of optic perineuritis.

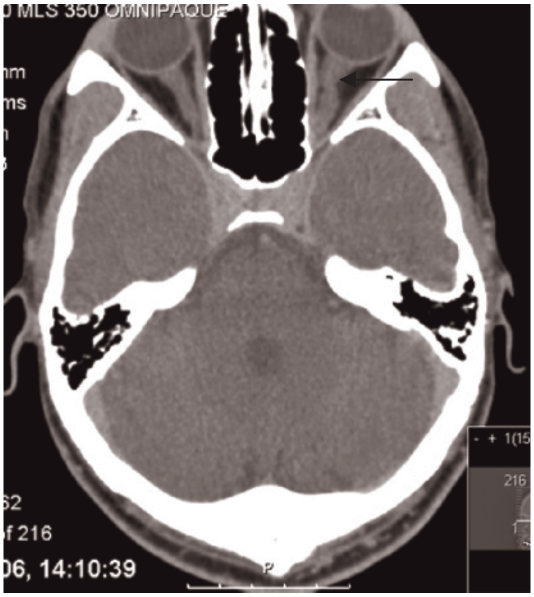

Figure 13.2 Thickened left optic nerve sheath in granulomatous optic neuropathy (sarcoid).

Treatment

In general terms, corticosteroids are used in the acute phase; it is essential that the treatment is given over weeks in slowly reducing doses. The treatment of neurosarcoidosis is reviewed in Chapter 25.

Optic neuritis: neuroretinitis

Clinical features

This condition presents in similar fashion to MS-AON but the pathology is clearly more anterior. The optic disc is swollen and within a few weeks a macular star develops. The macular star (exudates in a radial pattern around the macula) indicates that there has been oedema affecting the retina itself and it may be that this syndrome results from inflammation more of the retinal ganglion cell layer than of the optic nerve itself (Plate 13.3). It is an important diagnosis to make because it is not associated with MS.

Investigations

This disorder commonly occurs post-infection and therefore appropriate serological tests may be revealing (e.g. *Bartonella* infection – cat scratch disease). The optic nerve does not show swelling, increased T2 hyperintensity nor enhancement on gadolinium-enhanced MRI in acute neuroretinitis. Neither will there be any CNS abnormalities.

Treatment

Corticosteroids may or may not be used in the acute phase, depending upon the degree of visual impairment.

Optic neuritis: optic perineuritis

Clinical features

Optic perineuritis describes a condition in which the optic nerve is not directly involved in the inflammatory process, but rather the optic nerve sheath. Presentation can be much as any other form of optic neuritis but there may be considerable and sustained pain (in some cases the patient is reluctant to move the eye at all because of pain). There may be orbital signs of congestion or inflammation and disc swelling is almost universal. Peripheral visual field loss is more common than a central defect. The pathology is a meningeal-based process and is caused by infective disorders such as tuberculosis and syphilis or infiltration with a neoplastic process particularly lymphoma, or malignant meningitis. The condition may represent optic nerve involvement in a primary orbital inflammatory syndrome.

Investigations

MRI shows a thickened and enhancing optic nerve sheath often with involvement of the orbital fat. Investigations are directed towards excluding a systemic condition. Rarely, a biopsy of the optic nerve sheath may be necessary. CSF examination should include careful cytology for neoplasia.

Treatment

Treatment depends upon the exact cause if it can be determined. Many cases are idiopathic and all of the investigations must be carried out within 48 hours so that corticosteroid therapy can be instituted promptly if no other cause is found as any delay in treatment may result in a less favourable visual outcome.

Ischaemic ocular syndromes

Nosology of ischaemic syndromes

It is essential to have an understanding of the vascular supply to the intracranial and intraorbital portions of the optic nerve, to the optic nerve head and to the outer and inner layers of the retina. The ganglion cell layer of the retina is supplied in most individuals entirely by the central retinal artery which is a branch of the ophthalmic artery and is an end artery. Occlusion of this artery results in total visual loss and this is a common consequence of retinal embolism. In around 15% there is a branch of the choroidal circulation (cilioretinal artery) which is usually solitary and supplies the macula. Occlusion of this artery will give rise to a scotoma extending from the blind spot to the macula. This is a rare event in isolation but can occur in association with central retinal vein occlusion.

The prelaminar (most anterior) portion of the optic disc is supplied by the short posterior ciliary arteries which are several in number. These are also branches of the ophthalmic artery but are not end arteries because there is an anastomosis (the circle of Zinn–Haller) around the optic nerve itself immediately behind the globe where the arterioles pierce the sclera to supply the optic nerve head and the choroid. Ischaemic events in posterior ciliary retinal artery territory therefore are not related to embolic or arteriolar occlusive disease as is the case with the central retinal artery but to low perfusion. The optic disc is especially vulnerable in this respect because it is at a watershed between the supply from the internal carotid artery (via the ophthalmic artery) and the external carotid artery (via the numerous branches which supply orbital structures such as the facial artery and angular artery, the superficial temporal artery and the middle meningeal artery which anastomose with branches of the ophthalmic artery).

The anastomoses between the internal and external carotid artery in the orbit are extensive and for this reason occlusion of the ophthalmic artery in isolation does not result in any ischaemic consequence because the branches of the external carotid can take over the supply to all of the orbital structures. Similarly, occlusion of the internal carotid artery, in the presence of an adequate external carotid artery supply will not result in any ischaemic complications in the orbit and indeed the flow in the ophthalmic artery will be reversed.

The retrolaminar portion of the optic nerve and the remainder of the intraorbital nerve are supplied by pial vessels and by penetrating branches of the ophthalmic artery. The intracanalicular portion of the nerve is supplied by penetrating branches of the ophthalmic artery and the intracranial portion by pial vessels.

Central and branch retinal artery occlusion

Clinical features

In central retinal artery occlusion (CRAO) abrupt loss of vision may be reported or loss of vision noticed on waking. Occasionally, the loss of vision may go unnoticed by the patient, more commonly in branch retinal artery occlusion (BRAO; Plate 13.4). There is no pain. In BRAO the field defects respect the fact that the branch arterioles of the central retinal artery do not cross the horizontal raphe of the retina so that altitudinal defects, or portions thereof, are the rule. Any portion of the retina supplied by a cilioretinal artery (most commonly the macula) will be spared. Acutely, there is retinal oedema (cloudy swelling) which is the hallmark of infarction of the inner layers of the retina which includes the ganglion cell layer. The 'cherry red spot' at the macula is in fact normal in colour; it is simply that this is a zone that is free of capillaries and ganglion cells, hence the red spot results from the intact choroidal supply, thrown into contrast by the surrounding pale and infarcted retina (Plate 13.5). If flow in the central retinal artery is restored within a matter of minutes following the occlusive event, then transient monocular blindness will result. If it is restored some time later, when infarction has occurred, then the appearance of the fundus can return remarkably to normal except that there is total loss of the retinal nerve fibre layer.

Of particular value is the search for the various types of embolus – calcific, cholesterol (Plate 13.6) or platelet/fibrin – as this can give some clue as to the source of the embolus. Not all retinal artery occlusions are caused by embolic disease, however, and CRAO can occur in giant cell arteritis and other causes of vasculitis. Some cases are seen of recurrent BRAO and in this situation a more extensive vasculopathy should be suspected such as Susac's syndrome where recurrent arteriolar ischaemic events occur in the retina, the brain and the cochlea. Clearly, in these situations it is the systemic associated features that often give the clue (Chapter 25).

Investigations

If a calcific embolus is seen as a cause of a CRAO then a cardiac source should be suspected, whereas platelet/fibrin embolus or cholesterol is more likely to have originated in atheromatous disease of the ipsilateral internal carotid or aortic arch.

Treatment

Treatment of acute CRAO is attempted if seen early enough. Administering acetazolamide intravenously and performing ocular massage to lower intraocular pressure and improve perfusion is established practice but has no evidence base. Even cases with a blind eye for some hours can experience partial recovery spontaneously and it would be difficult to set up a controlled trial of such treatment. At the time of writing a European study of the efficacy of thrombolysis (by selective injection of a thrombolytic agent into the ophthalmic artery) is underway.

Central and branch retinal vein occlusion

Clinical features

Patients usually present complaining of painless abrupt onset of blurred vision or there may be no symptoms. The appearance of a central retinal vein occlusion (CRVO) is easily recognized – there is swelling of the optic disc and congestion of the retinal veins with extensive nerve fibre layer haemorrhages. Partial retinal vein occlusion can cause diagnostic confusion because the patient may present with unilateral disc swelling only and be investigated for raised intracranial pressure or an optic nerve tumour.

Investigations

For the neurologist the task is usually to exclude any underlying prothrombotic disorder in the absence of obvious vascular risk factors such as hypertension or diabetes. CRVO can occur in young fit people and dehydration may have a part to play in some of these. Otherwise, most studies have shown an association between CRVO and various vascular risk factors particularly when recurrent. There is no need for imaging but it must be remembered that some optic nerve tumours (particularly malignant glioma of the optic nerve) can present with a picture resembling a CRVO but in these cases there is usually progression of visual loss and progression to arterial occlusion.

Treatment

There is no treatment for the acute disorder but referral to the ophthalmologist is necessary because if there is significant retinal ischaemia new vessel formation can occur with all its attendant complications. Otherwise, management is limited to prevention of recurrence as with all occlusive vascular disease.

Non-arteritic anterior ischaemic optic neuropathy

Clinical features

Ischaemia at the level of the posterior short ciliary artery supply to the prelaminar optic nerve head results in anterior ischaemic optic neuropathy (AION). By definition, the optic disc will be swollen acutely. Indeed, it should always be insisted that the diagnosis is not made unless the patient was seen acutely and the disc observed to be swollen. The common form of AION is non-arteritic. The pathogenesis of this condition is not understood but the condition may be caused by a drop in the perfusion pressure of the optic nerve head. It is almost never brought about by embolic disease (with the rare exception of atrial myxoma). Associations therefore include systemic hypotension (especially blood loss, during surgery and during renal haemodialysis) and obstructive sleep apnoea/hypopnoea syndrome. The other factor that influences perfusion of the optic disc is intraocular pressure and angle closure glaucoma may precipitate AION.

The morphology of the optic disc is of particular importance, the majority of cases have small 'crowded' optic discs (usually also hypermetropic, i.e. the scleral opening is small and the optic nerve has little or no cup; Plate 13.7). Therefore, if a minor degree of ischaemia leads to swelling of the optic nerve head, the ischaemia will be exacerbated and lead to infarction.

In non-arteritic AION the most common field defect is a lower altitudinal one – hence the upper part of the optic disc is more vulnerable, a feature also in favour of the critical perfusion hypothesis. The optic disc will be swollen throughout initially but after 4–6 weeks the upper pole will become atrophic as the nerve fibres disappear while the lower pole remains swollen. A few weeks later sectoral optic atrophy is seen with loss of optic nerve fibre from the upper pole of the disc corresponding to the visual field defect (Plate 13.8).

Patients most commonly complain of sudden or subacute visual loss with some progression over hours to days, they may notice the loss on waking, or it may pass unnoticed until the visual field defect or optic atrophy is picked up some time later. AION rarely affects the same eye a second time but some cases show stepwise progression sometimes over many weeks. Unfortunately (and possibly related to the vulnerable optic disc morphology), there is a risk of the same process occurring in the other eye in about 20–40% of cases. Second eye involvement is usually within months to years, bilateral simultaneous involvement suggests systemic hypotension as the cause.

Investigations

Non-arteritic AION is rarely associated with embolic disease and only exceptionally associated with disease of the ipsilateral carotid artery (usually in the context of disease of both the internal and external carotid arteries and inadequate perfusion of the entire globe). Thrombophilic conditions (most of which cause venous rather than arterial occlusions) are rarely implicated. Investigations are limited to a general screen for vascular risk factors with consideration of nocturnal hypotension or obstructive sleep apnoea as cofactors.

Many patients with non-arteritic AION are relatively young and do not have extensive evidence of generalized vascular disease and in these patients the disc morphology may be the only predisposing factor.

Treatment

Management is treatment of any underlying cause and of general vascular risk factors. There is no treatment known to influence the visual deficit although drugs to lower the intraocular pressure are sometimes used. Neither has it been shown that prophylactic aspirin can reduce the risk to the other eye but it seems reasonable to prescribe it as general secondary prevention.

Anterior ischaemic optic neuropathy in giant cell arteritis and other vasculitides

There is an extensive literature on factors which help distinguish between arteritic and non-arteritic AION. The argument is centred on the need to diagnose giant cell arteritis (GCA) and to prevent blindness. While the importance of this cannot be overemphasized, the arteritic versus non-arteritic AION dichotomy is only a part of the story. It is essential to realize that AION is not the only cause of visual symptoms and visual loss in GCA, furthermore there are other systemic inflammatory conditions that can lead to AION.

Clinical features

By definition, all causes of AION will be associated with disc swelling but in GCA the loss of vision is more profound than in non-arteritic AION, indeed total blindness of the affected eye in a matter of hours is the rule. The swollen disc will look pale early – often within days – whereas in non-arteritic AION the disc only becomes pale as optic atrophy supervenes (Plate 13.9). Premonitory transient visual loss occurs in GCA but never in non-arteritic AION, this is not embolic but a result of poor perfusion. Usually patients are aware that the loss of vision lasts seconds only and tends to come on with change of posture from sitting or lying to standing. This phenomenon is related to the pathological difference between the two conditions. Indeed, all of the distinctions between the two can be explained in these terms.

First in GCA, many arteries and arterioles are involved, hence there is more extensive ischaemia. The central retinal artery and the choroidal vessels may be involved, the entire globe or indeed entire orbit may be ischaemic because branches of both the internal and external carotid artery are affected. Secondly, GCA is a vascular occlusive disorder which accounts for the more profound visual loss as there is no collateral or anastomotic supply which may help to preserve vision. However, in GCA, the occlusion is generally not thrombotic and the lumen is occluded by the intimal hypertrophy that is the pathological hallmark of the disease.

Apart from the severity of the visual loss, preceding symptoms – both visual and systemic – should be sought in any patient with visual loss that might be brought about by GCA. Headache and tenderness of the extracranial arteries (especially the superficial temporal and occipital arteries) are important clues to the diagnosis as is other evidence of ischaemia in the territory of the branches of the external carotid artery (ischaemic jaw pain on chewing, scalp or tongue necrosis). Polymyalgia rheumatica often occurs in the same individuals and may precede or follow GCA by some years. The disease is rare below the age of 50 years.

An often neglected clinical sign is the palpation of the superficial temporal, occipital and facial arteries (Plate 13.10). In a severe case of GCA these arteries will be thickened, pulseless and tender. In the appropriate clinical context this confirms the diagnosis. In other cases they may be normal or thickened but still with a pulse. False positives are possible because arteriosclerosis alone can result in similar findings.

AION can occur in other true vasculitides where there is inflammation in the vessel wall especially where arterioles are affected (e.g. polyarteritis nodosum, Churg–Strauss syndrome and ANCA positive vasculitis). It can also be seen where there is vascular occlusion because of antigen–antibody complex deposition in arterioles and capillaries such as in systemic lupus erythematosus. These conditions have characteristic systemic features but it is beyond the scope of this chapter to list them all. An important clinical point, however, is that these disorders lie somewhere between GCA and non-arteritic AION in their clinical features – visual loss may be intermediate in severity, for example. The importance in recognizing these conditions is that, unlike non-arteritic AION and the vast majority of cases of GCA, there is some possibility of visual recovery if treatment is administered promptly.

Investigations

A normal ESR and C-reactive protein (CRP) do not exclude the diagnosis but in most cases these are reliable screening tests with all the usual concerns regarding false positive and false negative results. In clinically definite cases of GCA there is no particular need to rely on blood tests apart from monitoring treatment. A biopsy should be carried out if possible because it is always helpful to future management to have that result in the notes (Plate 13.11). In doubtful cases urgent ESR, CRP, platelet count and the gamma GT (thrombocytosis and abnormal liver function tests are quite often found in GCA) should be undertaken before proceeding to a temporal artery biopsy. The rapidity of the response of headache to steroids (usually measured in hours after the first dose) is also useful circumstantial evidence.

Treatment

Therapy with corticosteroids, at 1 mg/kg body weight, should be commenced urgently in any suspected case of GCA. Intravenous methylprednisolone to initiate therapy may have advantages. There is a time window of a few days in which visual loss can occur in the other eye even after treatment with steroids has been initiated. A delay of even hours can make a difference in preventing blindness. Unfortunately, the chances of recovery in an eye already showing signs of AION are low. It is possible to demonstrate that the lumen recanalizes in affected arteries – simply by palpating the superficial temporal arteries again in a week or two when the pulse will be restored. In clinical practice the main problem is the need to minimize the adverse effects of corticosteroids and discontinue the treatment safely without risking relapse.

Posterior ischaemic optic neuropathy

Posterior ischaemic optic neuropathy (PION) should not be diagnosed except in the context of GCA and systemic hypotension as it is much more common (and has potentially more serious consequences) for a compressive disorder to be erroneously diagnosed as PION than the other way around.

Clinical features

There is subacute painless loss of vision with variable patterns of visual field loss with, in the acute phase, a normal fundus and optic atrophy developing later. Where visual loss has occurred in the context of spinal surgery or blood loss the loss of vision is more likely to be bilateral (see below).

Investigations

In the appropriate context the comments apply as above for arteritic AION. In recovery from peri-operative visual loss little needs to be done except to exclude an unlikely compressive lesion by appropriate imaging. There is little information on the MRI appearances of the optic nerve in acute PION, there is no need to carry out this investigation in GCA and cases of spontaneous PION are very rare. There is often high signal and gadolinium enhancement of a segment of the nerve.

Treatment

Treatment of GCA is discussed above. There is no treatment for PION in other contexts.

Chronic ocular ischaemic syndromes

Clinical features

In a number of situations there may be chronic ischaemia of the retina, the optic disc or the entire globe.

As far as the optic disc is concerned chronic ischaemia at the capillary level will lead to disc swelling with a variable degree of visual loss; the classic example is known as 'diabetic papillopathy' where a chronically swollen disc is seen in poorly controlled diabetes. Disc swelling in accelerated hypertension has a similar aetiology and can persist for some time without significant loss of vision. In both instances there is a risk of infarction of the optic nerve which will lead to permanent loss of vision. In the case of accelerated hypertension this may occur if the blood pressure is treated too aggressively.

'Slow flow retinopathy' is seen when there is poor perfusion of the retina. Patients may complain of transient loss of vision, particularly associated with change from a sitting to a standing posture and on moving to bright illumination particularly sunlight. On examination, vision may be only mildly impaired but there is congestion of retinal veins, haemorrhages in the mid-periphery (characteristically petal-shaped) and macular oedema. The central retinal artery collapses with minimal digital pressure on the globe and indeed may show spontaneous pulsation because in diastole the pressure is lower than the intraocular pressure. In more severe cases the entire globe may be ischaemic, this leads to the formation of new vessels at the iris – rubeosis – which in turn leads to glaucoma. This situation occurs when there is severe impairment of both the internal and external carotid artery supply to the orbit.

Investigations

The task is to confirm that the problem is with occlusion of the ipsilateral carotid artery. The principal differential diagnosis is GCA which can also give rise to an ocular ischaemic syndrome as explained above.

Treatment

The evidence that carotid endarterectomy is effective in these disorders is not compelling and many cases, if followed, will not deteriorate nor develop significant visual loss, except in the case of rubeotic glaucoma which should be treated by an ophthalmologist.

Tumours affecting the optic nerve

Compressive or infiltrative optic neuropathy

Visual loss may be unilateral or bilateral. In unilateral cases there will be a relative afferent pupillary defect, the disc may be normal, swollen or infiltrated. When the visual impairment is bilateral the lesion is almost always intracranial or in the paranasal sinuses and the optic discs appear normal at presentation although progressive loss of colour vision and an afferent pupillary defect may occur. The disc may develop collateral vessels to bypass the retinal circulation. Locally invasive tumours such as optic glioma and optic nerve sheath meningioma compress the optic nerve and directly cause axonal backflow. Systemic malignancies such as leukaemia, lymphoma and metastases can directly infiltrate the optic nerves usually via the dura and cause both compression and papilloedema leading to more abrupt or rapidly progressive visual loss (Table 13.7).

Primary optic nerve meningiomas

Primary optic nerve meningiomas arise from the arachnoid cells of the optic nerve sheath. Their origin is generally in the orbital portion of the nerve. Intracranial extension of primary optic nerve sheath meningioma may occur. Primary optic nerve sheath meningiomas are more common in middle-aged females and are generally unilateral but may be bilateral or multifocal particularly in neurofibromatosis type II. They may present with features of a slowly progressive optic neuropathy leading to loss of acuity, impairment of colour vision with a central scotoma and a relative afferent pupillary defect. Fundal examination shows unilateral optic atrophy but there may be chronic disc oedema with retinochoroidal venous collateral vessels indicating chronic retinal vein obstruction. The management of primary optic sheath meningioma is controversial as visual loss is likely regardless of treatment and intracranial extension is rare (Fig. 13.3).

Other forms of meningiomas

Meningiomas may arise from the sphenoid wing, tuberculum sellae or olfactory groove. They cause visual failure by direct compression of the intracranial portion of the optic nerve or

Table 13.7 Causes of compressive and infiltrative optic neuropathies.

Compressive	
Tumour	Intraorbital tumours
	Optic nerve sheath meningioma
	Sphenoid wing meningioma
	Pituitary tumour
	Craniopharyngioma
Non-neoplastic	Thyroid eye disease
	Sphenoid mucocoele
	Orbital pseudotumour
	Orbital haemorrhage
	Paget's disease
	Fibrous dysplasia
Infiltrative	
Neoplastic	Optic nerve glioma
	Metastatic carcinoma
	Nasopharyngeal carcinoma
	Lyphoma
	Leukaemia
	Meningeal carcinomatosis
Non-neoplastic	Sarcoidosis

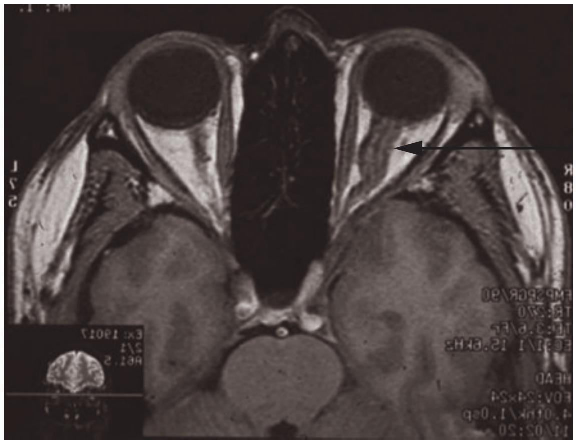

Figure 13.3 Perioptic meningioma (arrow).

chiasm but they may invade the optic canal and orbit. Large olfactory groove or sphenoid wing meningiomas can cause optic atrophy in one eye due to compression and papilloedema in the other eye due to raised intracranial pressure (Foster Kennedy syndrome). Imaging of splenoid wing meningioma shows sphenoid hyperostosis and contrast enhancement on CT if there is orbital extension of the intracranial mass. Surgical excision is a treatment of choice for sphenoid wing tumours if there is significant visual loss.

Optic and optochiasmal glioma

Primary glial tumours of the anterior visual pathway (optic glioma) occur either as benign gliomas of childhood or rarely as malignant glioblastoma in adults.

Benign optic gliomas of childhood arise in the chiasm more often than within the orbit or the canal. Patients present with proptosis and visual field loss which is generally bilateral and either scotomatous or bitemporal. There may be horizontal or rotatory nystagmus with head nodding. The optic disc is swollen or atrophic leading to fluctuations in visual function which may improve spontaneously in some patients (Plate 13.12). It is essential to exclude neurofibromatosis type I. Optic glioma of childhood may be associated with hypothalamic or thalamic involvement and there may be hydrocephalus or signs of raised intracranial pressure and leptomeningeal spread may occur. The management is controversial as these tumours are slow-growing. Surgery is confined to palliative treatment for intraorbital tumours and chiasmal gliomas. Radiotherapy results in significant tumour shrinkage and improvement in visual function but carries a risk of radionecrosis of the optic nerve. However, surgical intervention may be required for hydrocephalus, decompression of intraneural cyst or biopsy.

Primary malignant gliomas of the optic nerve generally arise in males aged 40–60 years and patients present with rapid monocular visual loss, retrobulbar pain and disc oedema with transient improvement on corticosteroids, signs mimicking optic neuritis. However, within several weeks of treatment visual function deteriorates again and contralateral visual loss develops. There may be an associated central retinal vein or artery occlusion as a result of vascular compression. Radiotherapy and adjunctive chemotherapy may slow progression somewhat but spread along the optic nerve sheath usually occurs within a few months with a uniformly poor prognosis.

Hereditary optic neuropathies

Autosomal dominant optic atrophy

Autosomal dominant optic atrophy typically commences in childhood or the teenage years and is characterized by insidious binocular visual loss which is highly variable. It commonly affects the papillo-macular nerve fibre bundle causing loss of central vision manifest as impaired visual acuity with a bilateral symmetrical central or centro-caecal scotoma and mild impairment of colour vision. Optic atrophy is often localized to the temporal portion of the optic nerve (Plate 13.13) and there may be associated sensorineural hearing loss. The condition is transmitted as an autosomal dominant with high penetrance although there is variability even within families. The gene responsible (OPA1) is located on the long arm of chromosome 3 although there is considerable genetic heterogeneity.

Leber's hereditary optic neuropathy

Leber's hereditary optic neuropathy (LHON) typically presents in young adults with subacute painless loss of central vision which develops over 3–6 months; however, there is considerable variability in the age of onset and rate of progression. While the onset may be bilateral and symmetrical, in up to 50% of patients one eye is affected initially followed by similar loss in the fellow eye developing within 4–6 weeks. The rate of visual loss is considerably quicker than in dominant hereditary optic atrophy and progressively worsens over several weeks although sudden and complete visual loss may occur.

On examination there is marked impairment of visual acuity and colour vision, with a central or centro-caecal scotoma with preservation of the peripheral field (Figure 13.4). The disc may

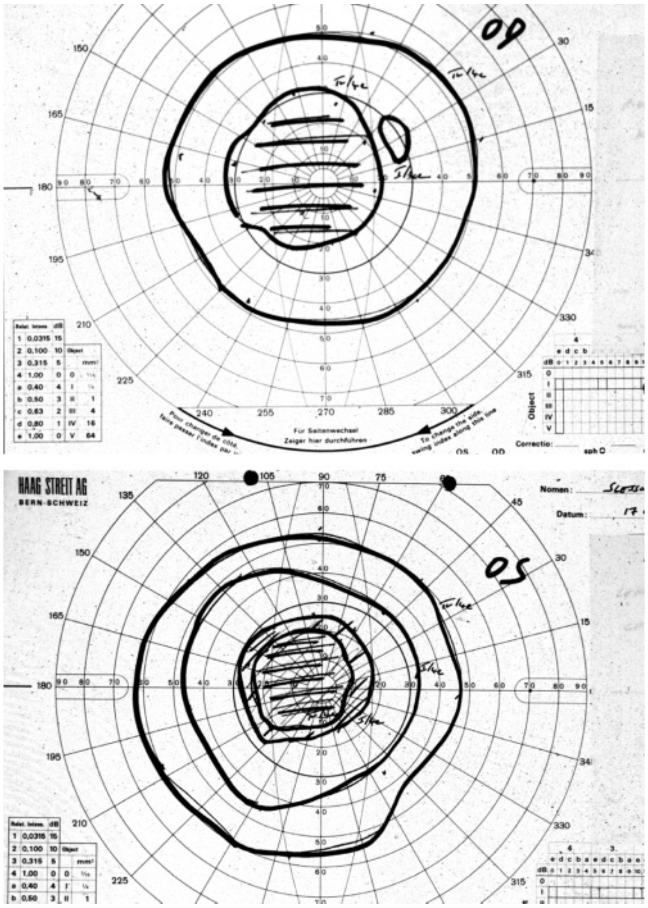

Figure 13.4 Bilateral central scotomata in Leber's hereditary optic neuropathy.

appear normal but the condition is characterized by a triad of hyperaemia with swelling of the optic nerve fibre layer around the disc ('pseudopapilloedema'), telangiectatic vessels on the disc and in the circumpapillary region and the absence of leakage on fluorescein angiography. Optic nerve involvement progresses to optic atrophy with non-glaucomatous cupping, pallor and attenuation of the arterioles (Plate 13.14). The optic disc abnormalities may be present for many years prior to the onset of visual loss and may be seen in unaffected carriers of the mutation.

Some patients may have cardiac conduction defects or other neurological features including pyramidal signs with brisk reflexes, cerebellar ataxia and tremor, movement disorders, distal sensory neuropathy or encephalopathy and some patients have been reported to develop MS. It is therefore important to exclude LHON in patients with severe visual loss resulting from MS. The prognosis for restoration of vision is poor but some patients do recover vision spontaneously many years later.

LHON is a mitochondrial disorder which is maternally inherited. It is caused by point mutations within the mitochondrial genome at nucleotide positions 11778, 3460 and 14484 in genes that encode subunits of the respiratory chain. The 11778 mutation is the most common and has the worst visual prognosis with a 4% improvement rate. However, 25–40% of patients with mutations at sites 14484 and 3460 experience improvement in visual acuity and the field deficit.

It is important to consider the diagnosis in any patient with painless, relatively rapid visual loss particularly with an asymmetrical onset and to distinguish the condition from toxic nutritional optic neuropathy.

Toxic nutritional optic neuropathies

Toxic nutritional neuropathies are often considered together because it is difficult to distinguish the relative contribution, particularly in tobacco- or alcohol-related amblyopia. Clinically toxic and nutritional deficiencies present with subacute bilateral central visual loss with impaired acuity, centro-caecal scotoma and impaired colour vision. Toxic and deficiency optic neuropathies are almost always bilateral although one eye may be affected before the other. The optic disc appears hyperaemic at onset but temporal pallor develops as a later finding and there is selective vulnerability of the papillo-macular bundle. The loss of vision usually evolves slowly over months, with moderate to severe impairment of acuity although complete blindness may result from methanol toxicity.

Tobacco-alcohol amblyopia is usually associated with excessive tobacco consumption with or without alcoholism or poor nutritional intake. A similar syndrome is associated with vitamin B_{12} deficiency and may occur with vitamin B_{12} levels that remain in the low normal range. Nutritional optic neuropathy may occur in a number of settings including chronic alcohol abuse, starvation, malabsorption syndromes or depression.

Toxic amblyopia (Chapter 18) is particularly associated with amiodarone, ciclosporin and digoxin and may develop with other neurological manifestations including peripheral neuropathy, ataxia and tremor. In Cuban epidemic optic neuropathy there is an associated peripheral neuropathy, myelopathy and sensory neural hearing loss.

Traumatic optic neuropathy

Traumatic optic neuropathy follows blunt head trauma usually associated with impaired consciousness. It results from damage to the optic nerve and its blood supply from haemorrhage and swelling (Plate 13.15). Visual loss is variable but may be severe. There is no evidence for improvement following corticosteroids or decompression of the optic nerve within the optic canal.

Radiation-induced optic neuropathy (Chapter 18)

This can occur in up to 15% of patients who have received radiotherapy with doses up to 5000 cGy but may occur with smaller doses if there has been coexisting chemotherapy or diabetes mellitus. Visual loss occurs 4–8 years after radiotherapy with a relatively rapid progression in one or both eyes. The optic disc is initially normal but pallor develops. There is no effective treatment despite trials of corticosteroids, anticoagulants and hyperbaric oxygen therapy. A transient and self-limiting form may occur which is usually treated with corticosteroids.

Optic disc oedema

Optic disc swelling (Table 13.8) is the end result of many pathological processes. A swollen disc implies axonal distension and elevation of the optic disc while disc oedema suggests axonal swelling. Papilloedema is indicative of elevated intracranial pressure.

It is important to distinguish papilloedema from bilateral anomalous disc appearances. Local causes for disc swelling (e.g. optic neuritis, ischaemic optic neuropathy and compressive lesions) are frequently unilateral and often present with ipsilateral visual loss and a relative afferent pupillary defect.

Table 13.8 Optic disc swelling with preserved or limited impairment of optic nerve function.

- Papilloedema (increased intracranial pressure)
- Compressive/infiltrative orbital process
  - Tumour
  - Graves' disease
  - Inflammation – often perineuritis
- Central retinal vein thrombosis
- Benign optic disc vasculitis
- Toxic optic neuropathy
- Malignant hypertension
- Posterior uveitis
  - Sarcoidosis
  - Low intraocular pressure

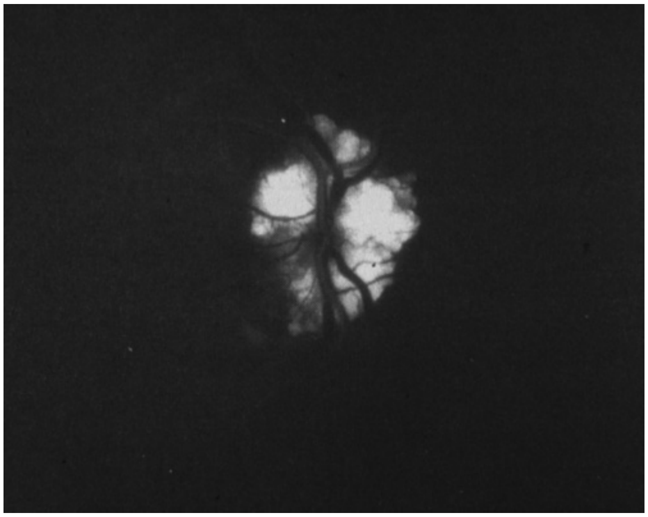

Figure 13.5 Optic disc drusen demonstrated by autofluorescence.

Specific optic disc anomalies

Optic disc drusen

These are small hyaline concretions on the surface or 'buried' beneath the optic nerve head causing elevation of the optic disc but no other features of true swelling. They are usually bilateral and drusen may be easily visible. Up to 70% of patients have a field defect including enlargement of the blind spot and arcuate or infero-nasal defects but central vision is preserved. Drusen may be associated with retinitis pigmentosa and are transmitted as an autosomal dominant trait (Fig. 13.5; Plate 13.16).

Tilted disc

This is a non-hereditary condition characterized by bilateral elevation of the supero-temporal disc, posterior displacement of the infero-nasal disc, situs inversus of the retinal vessels and bitemporal visual field defects. The elevated superior disc may be mistaken for segmental swelling but there is no hyperaemia or obscuration of the peri-papillary vessels.

Myelinated nerve fibres

These appear as white striated patches, often at the upper and lower poles of the optic disc, which typically spare the papillomacular bundle. They rarely affect acuity or visual field (Plate 13.17).

Papilloedema

Papilloedema is the most common cause of optic disc swelling without visual loss and is caused by raised intracranial pressure (Plate 13.18). This may occur as as a result of the following:

1 An intracranial mass, e.g. tumour, abscess or haemorrhage;
2 Excessive production of CSF (i.e. choroid plexus papilloma);
3 Blockage of arachnoid villi by blood or protein (e.g. infection, sarcoidosis, carcinomatous meningitis);
4 Obstruction of flow of CSF through the ventricles (e.g. aqueduct stenosis);
5 Decreased flow of venous blood through the dural sinuses (venous sinus thrombosis);
6 Idiopathic intracranial hypertension (see below).

Patients with papilloedema may present clinically with transient binocular visual obscurations which occur occasionally or many times a day and are often related to changes in posture. There may be diplopia caused by unilateral or bilateral VIth nerve palsy. In the early stage visual loss only occurs if haemorrhages, exudates and oedema develop over the macula or in the subretinal fluid or if there is a mass lesion involving the optic nerve or chiasm. On examination the visual field is initially normal but as disc swelling worsens, there is an enlarged blind spot. If intracranial pressure is severe enough to cause compression and axonal loss an arcuate scotomatous defect develops and with continued damage generalized field constriction occurs although visual acuity remains preserved unless the field loss is severe. It is unclear why the papillomacular bundle (i.e. the portion of the ganglion cell layer subserving central vision) is spared until late.

The disc appearance varies with severity. In early papilloedema there may be only mild swelling of the optic disc with no evidence of haemorrhages or dilation of retinal veins (Plate 13.19). However, as papilloedema worsens the discs become increasingly swollen and hyperaemic and the vessels become obscured by swollen tissues and spontaneous venous pulsation is lost. Peripapillary flame-shaped haemorrhages may appear with folds in the retina and/or macula which rarely compromise vision. When papilloedema is fully developed visual acuity and colour vision are normal but the blind spot is enlarged and severe field constriction is present. With chronic papilloedema the discs become pale and the margins clearer, haemorrhage resolves but the constricted visual field persists (Plates 13.20–13.22). Eventually atrophic papilloedema occurs when the swelling has resolved and led to the death of nerve fibres. The optic discs are pale, visual acuity is reduced and the visual fields are severely constricted.

Papilloedema can only develop if there is patency of the subarachnoid space surrounding the optic nerve. If these spaces are blocked by adhesions, papilloedema does not occur. Loss of the nerve fibres in optic atrophy will also prevent the development of papilloedema. Development of papilloedema apparently depends on increased pressure in the distal optic nerve sheath, decreased perfusion of the axons exiting through the lamina cribrosa and possibly elevated central retinal venous pressure. Disturbance of both slow and fast axoplasmic transport are a feature of papilloedema (Plate 13.23).

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension (IIH) is a disorder of elevated intracranial pressure of unknown cause which may lead to visual loss due to papilloedema. The condition usually occurs in obese women of childbearing age.

The diagnosis depends on fulfilling the modified Dandy criteria:

1 Symptoms and signs of elevated intracranial pressure in an awake and alert patient.
2 No localizing symptoms or signs other than a VIth nerve palsy.

3 Normal neuroimaging (apart from changes due to the raised pressure itself).
4 Lumbar puncture showing elevated opening pressure (>250 mm/H_2O) but normal fluid analysis.

Intracranial hypertension may be idiopathic or may develop secondarily to a number of underlying conditions, particularly venous sinus thrombosis. The clinical features of idiopathic and secondary intracranial hypertension may be identical. However, the treatment of the secondary form depends on the underlying cause and it is therefore extremely important to exclude another underlying cause before making a final diagnosis of IIH.

Clinically, IIH presents with headache in >90% of patients, it is characteristically severe, daily and pulsatile; nausea and vomiting may be present. There may be retrobulbar pain with eye movements and radicular pain in the neck and shoulders radiating down the arms. Transient visual obscurations lasting for seconds or minutes and associated with postural changes are present in up to 70% of patients. Tinnitus is common and some patients develop hearing loss. Diplopia, usually horizontal is present in up to 40% of patients usually resulting from a VIth nerve palsy. Other symptoms include incoordination, impaired sense of smell and numbness or motor weakness.

On examination only 15% of patients who present with IIH have impairment in visual acuity but significant visual field loss is common. An afferent pupillary defect suggests asymmetric visual loss and is present in the eye with the greatest amount of field loss. Ocular motor disturbances such as esotropia and esophoria may be present. VIth nerve palsies are relatively common because of stretching of the nerve by intracranial hypertension. A IIIth nerve palsy may occur in IIH but other causes must be excluded. Signs of optic disc swelling include elevation and blurring of the disc margin, a peri-papillary halo, venous congestion and tortuosity, retinal exudates and retinal infarct (cotton wool spots). Significant visual loss is likely with nerve fibre layer haemorrhages, subretinal neovascularization, cotton wool spots, choroidal folds or macular oedema. Papilloedema may be unilateral or asymmetrical, and optic nerve atrophy suggesting long-standing papilloedema may be present in up to 10% of patients. The appearances may be striking enough to mimic Foster Kennedy syndrome or AION.

Visual field abnormalities are frequent; enlargement of the blind spot and constriction of the fields are the most common manifestation. Other visual field defects include arcuate or centrocaecal scotomatous lesions, nasal visual field loss or loss of visual acuity alone. Visual field testing shows a greater sensitivity when compared with visual acuity and contrast sensitivity.

Venous sinus thrombosis leads to increased pressure within the dural sinuses which, in turn, causes poor absorption of CSF through the arachnoid granulations leading to papilloedema and headache. Venous sinus thrombosis is discussed in Chapter 4. The most important causes include hypercoagulable states (e.g. protein C and S deficiency, antithrombin III defiency and antiphospholipid Ab), thrombocythaemia, Behçet's disease, oral contraceptive use, pregnancy, local infection, iatrogenic trauma (e.g. subclavian vein thrombosis following catheter insertion) and mass lesions in the venous sinus (e.g. meningioma, metastases or cystic lesions).

IIH has been associated with a number of aetiological factors although clear evidence of a causal relationship is lacking. Endocrine disorders are likely to be important because of the strong female bias, association with obesity and the relationship of IIH to hypoparathyroidism and thyroid disorders, Addison's disease and Cushing's disease. IIH is also associated with obstructive sleep apnoea, medications including antibiotics (naladixic acid, ciprofloxacin, tetracyclines, minocycline and nitrofurantoin), hormonal medications including growth hormone and the oral contraceptive, and corticosteroids. The strongest link of IIH is with hypervitaminosis A or retinoid excess. Stopping the medication relieves the symptoms.

Investigations

MRI shows that up to 70% of patients have an empty sella, presumably caused by long-standing effects of pulsatile high-pressure CSF causing downward herniation of the arachnoid through a defect in the diaphragm sellae. Other features include reversal of the optic nerve head, flattening of the posterior sclera, enhancement of the prelaminar optic nerve, distension of peri-optical subarachnoid space, vertical tortuosity of the orbital optic nerve and intraocular protrusion of the prelaminar optic nerve.

Poor prognostic features for visual loss include long-standing swelling of the optic disc with atrophy, visual field or acuity loss at first examination, delay in treatment, systemic hypertension, age, male gender and increased intraocular pressure. Pre-existing disc anomalies such as drusen and an optic pit may also worsen the prognosis for visual outcome.

Management

Medical treatment of the underlying condition includes weight loss with restriction of calorie, salt and fluid intake. Repeat lumbar punctures may be necessary and in self-limiting disease this approach may tide patients over until spontaneous remission.

Symptomatic therapy is routinely used. Acetazolomide is a strong carbonic anhydrase inhibitor that reduces CSF production and is highly effective in IIH. The dose is gradually increased to 0.5 to 1 g/day although higher doses are occasionally necessary. Many patients develop evidence of toxicity with digital or peri-orbital tingling, anorexia or a metallic taste. Other diuretics such as bendrofluazide and frusemide can be used if acetazolomide is not tolerated. High-dose corticosteroids are normally only given in rare instances of severe visual failure in the short term, prior to CSF diversion surgery. The use of corticosteroids is controversial.

Surgical options, when required for intractable headache or progressive visual loss, include shunting and optic nerve sheath decompression (ONSD). The preferred shunt technique (normally either lumbar–peritoneal or ventricular–peritoneal) varies according to local expertise but effective shunting remains the best way of controlling headache and/or severe visual loss. ONSD is often used in instances when headache is minimal and visual loss is less severe, meaning that more invasive shunting procedures can be avoided.

Ocular involvement in other neurological disease

Uveomeningitic syndromes

Uveomeningitic syndromes are a group of disorders in which there is involvement of the uveal tract (either the iris, ciliary body or the choroid), the retina and the meninges. The causes are listed in Table 13.9.

Sarcoidosis (Chapter 25)

Up to 60% of patients with sarcoidosis may have ocular involvement and this may be the presenting feature. Conjunctival nodules and uveitis are commonly associated conditions and posterior segment inflammation is particularly seen with neurological involvement. The optic nerve appears swollen because of the intraocular inflammation but may be directly involved by granulomas or meningeal change. Retinal abnormalities in sarcoidosis include periphlebitis, haemorrhages and choroidal granulomas.

Behçet's disease (Chapter 25)

Ocular involvement may be caused by an ischaemic optic neuropathy or papilloedema secondary to venous sinus thrombosis. However, inflammatory ocular disease can occur in up to 70% of patients and this usually develops many years after the onset of neurological disease although it occasionally can be a presenting feature. There is usually a bilateral panuveitis with varying degrees of anterior and posterior segment involvement. Retinal vein occlusion may lead to optic atrophy and visual loss. There may be a venous retinal perivasculitis or retinal infiltrates and macular oedema. In Behçet's syndrome the visual prognosis is poor and ocular involvement responds poorly to immunosuppressant medication.

Table 13.9 Causes of uveomeningitic syndromes.

Inflammatory	Vogt–Koyanagi–Harada Sarcoidosis Beçhet's syndrome SLE Wegener's granulomatosis
Infections	*Borrelia*, syphilis, TB, leprosy, *Neisseria meningitidis* Fungi – *Candida*, coccidiodomycosis CMV, herpes simplex, HZV, HIV, hepatitis B SSPE
Neoplasia	Primary B-cell lymphoma Large cell or intravascular lymphoma Leukaemia Metastatic carcinoma, paraneoplastic
Primary ophthalmological	Acute posterior multifocal placoid pigment epitheliopathy Multiple evanescent white dot syndrome Posterior scleritis

CMV, cytomegalovirus; HZV, herpes zoster virus; SLE, systemic lupus erythematosus; SSPE, Subacute sclerosing panencephalitis; TB, tuberculosis.

Vogt–Koyanagi–Harada disease

Vogt–Koyanagi–Harada disease (VKH) is a granulomatous multisystem inflammatory disorder that affects the eyes, the auditory system, meninges and the skin. The cause is unknown. There may be meningism, tinnitus and a CSF pleocytosis; skin involvement is characterized by alopecia, poliosis (whitening of the eyebrows) and vitiligo. Early ocular involvement is characterized by uveitis and serous retinal detachment. Late manifestation is usually bilateral and includes choroidal and retinal depigmentation.

Multiple sclerosis

In MS (Chapter 10) the most common ocular manifestation is optic neuritis; however, symptomatic uveitis may occur in up to 3% of patients and asymptomatic changes are seen in up to 20%. Retinal vascular change including periphlebitis and sheathing or cuffing of the retinal veins with lymphocytes and plasma cells is also described. Visual loss in MS is therefore not always a result of optic neuritis but may rarely be caused by uveitis with macular oedema, previous haemorrhage or retinal vascular change with neovascularization.

Retinitis pigmentosa

Retinitis pimentosa may occur as an isolated genetic defect or as part of a variety of other diseases in particular mitochondrial disorders (Table 13.10). Isolated hereditary forms of retinitis pigmentosa may be autosomal recessive (<60%), autosomal dominant (<25%) and rarely X-linked. The X-linked and recessive forms are probably more severe than the autosomal dominant form. More than 20 genes coding for this disorder have now been recognized but the most common abnormality lies in the genes for rhodopsin and peripherin.

The initial loss in the rod dystrophy form of retinitis pigmentosa occurs in the mid-peripheral visual field with an inability to see as clearly in dim light as in bright light (nyctalopsia). There is then a progressive loss of the peripheral visual field. The fundus initially shows a grey discoloration of the retinal pigment epithelium but with progression pigmented cells migrate into the retina leading to a characteristic bone spicule appearance with 'waxy' pallor of the optic nerve and attenuated retinal vessels.

In contrast cone dystrophies are due to involvement of the photoreceptors in the region of the macula. These cause blurred vision and an inability to see as clearly in bright light as in dim light. There is loss of the central field of vision manifest as a reduction in visual acuity or a central scotoma with loss of colour vision. Initially the fundus appears normal but as the condition progresses there is pigmentary degeneration of the macular

Table 13.10 Causes of retinal involvement in neurological disease.

Retinitis pigmentosa	Hereditary Neurodegenerative disorders – abetalipoproteinaemia (Bassen–Kornzweig syndrome), Refsum's disease, adrenoleucodystrophy
Salt and pepper retinopathy	Kearns–Sayre syndrome Hallervorden–Spatz disease
Cone–rod dystrophy	Multiple system atrophy Spinocerebellar atrophy Juvenile Batten's disease
Cherry red spot	Tay–Sachs disease Niemann–Pick disease Sialidosis
Paraneoplastic retinopathy	Cancer-associated retinopathy Melanoma-associated retinopathy
Viral retinitis	Acute retinal necrosis

('bull's-eye maculopathy'). Eventually, optic disc pallor develops which mimics primary optic nerve disease.

Retinal pigmentary changes are associated with several forms of mitochondrial disease including NARP (neurogenic muscle weakness, ataxia and retinitis pigmentosa), MELAS (myoclonic epilepsy, lactic acidosis, stroke-like episodes) and Kearns–Sayre syndrome. In NARP retinal involvement is manifest as a cone rod dystrophy with variable involvement of each form of photoreceptors. The severity of the disease correlates with the extent of the mutation in mtDNA. Pigmentary change is noted in the first or second decade of life and associated with bilateral symmetrical ptosis. The macula is often affected initially followed by the peripheral retina with pigment clumping, atrophy and a 'salt and pepper' retinopathy. The visual acuity and fields are only mildly affected. There may be systemic and neurological involvement (Chapter 9). Retinal involvement has also occasionally been reported in subacute necrotizing encephalopathy (Leigh's disease) which is also ascribed to a mitochondrial respiratory chain deficiency. Retinitis pigmentosa has also been associated with a variety of metabolic abnormalities affecting amino acid protein or lipoprotein metabolism (Chapter 18).

Neoplasia

Metastatic disease is the most common form of intraocular malignancy. Lesions may involve the choroid, retina or vitreous humor. The lung and breast are the most common primary sources. Primary intraocular lymphoma occurs in up to 25% of patients with primary CNS lymphoma but ocular involvement may occur in isolation. Ocular lesions are variable. There may be a posterior uveitis with vitreous cellular infiltration. The characteristic lesion is a subretinal infiltrate which appears creamy yellow and is associated with retinal pigment epithelial detachment. There may be discrete pale retinal lesions or vascular changes including vasculitis. Paraneoplastic syndromes include carcinoma-associated retinopathy in which a progressive subacute bilateral visual loss is associated with pigmentary retinal change and arteriolar narrowing with sheathing.

Phakomatoses

Neurofibromatosis type I is associated with optic glioma and Lisch nodules which are hamartomas of the pigment epithelium. Retinal involvement is rare but there may be pigmentary change or capillary haemangiomas and neurofibromas of the uveal tract may occur. In neurofibromatosis type II, cataracts and retinal changes (hamartomas and pigment epithelial change) are seen but Lisch nodules are less common. In tuberous sclerosis hamartomas of the retina are prominent and may be present in up to 50% of patients, frequently bilateral. They do not interfere with visual function and the appearances are variable. They are generally semi-transparent but may be opaque and tend to calcify over time. Von Hippel–Lindau Disease (VHL) is associated with retinal capillary haemangiomas which appear as circumscribed round lesions. They are associated with large and developed feeder vessels eventually causing retinal detachment. They are usually situated in the retinal periphery but may develop around the optic disc. The present of multiple retinal capillary haemangiomas is diagnostic of VHL disease. In Sturge–Weber disease glaucoma is common but choroidal angiomas may affect one or both eyes.

Diplopia

Disturbances of eye movements may occur as a consequence of either reduced or excessive ocular motility. Diplopia results from dysfunction of the extraocular muscles, due to local factors; impairment of neuromuscular junction; disturbance of the cranial nerves at any point throughout their long course; or lesions at a nuclear or supranuclear level within the brainstem or central pathways. Oscillopsia (illusory visual movement) results from nystagmus or saccadic intrusion. Binocular diplopia is caused by ocular misalignment and therefore resolves if one eye is covered and is absent if there is severe monocular visual impairment. Monocular diplopia persists if one eye is closed and is generally caused by local eye disease, refractive error or functional disorders.

The character and pattern of diplopia should be established by history and examination. It is important to clarify whether the separation of images is maximal on vertical, horizontal or oblique gaze, whether any corrective head position is favoured and whether the diplopia is worse at a distance, (typically in a VIth nerve palsy) or for near objects (e.g. medial rectus palsy). Diplopia is worse when looking in the field of action of a paretic muscle or in the opposite field to a restricted muscle (i.e. when it is being stretched). Diplopia may be absent, despite ocular misalignment, if there is impaired acuity in one eye, if the separation is particularly wide or narrow and the false image can be suppressed or if the ocular misalignment is long-standing or has been present from birth. The presence of pain on eye movement suggests a local orbital or myopathic process while orbital or peri-orbital pain is characteristic of vascular, neoplastic, inflammatory or infective disorders.

The principles of examination of the extraocular movements are outlined in Chapter 3. The presence of pupillary asymmetry or impaired reactions may be important (e.g. fixed dilated pupils may indicate parasympathetic involvement in a compressive IIIrd nerve palsy). Involvement of other cranial nerves (e.g. II, V, VII and VIII) is important in localizing lesions and a proptosis suggests thyroid opthalmoparesis or a structural lesion of the orbit. Ocular alignment should be assessed by the corneal light reflex or cover test and the eye movement examination includes assessment of ocular motility in each eye in the nine positions of gaze. The presence of associated local factors (e.g. orbital swelling or dry eyes) or neurological features (e.g. other cranial nerve lesions) may be of localizing importance.

Vertical diplopia is present when the patient sees two images displaced vertically or diagonally and suggests impairment of any or all of the superior or inferior recti or oblique muscles. Torsional diplopia from underaction of the oblique muscles is associated with an angular head tilt. Horizontal diplopia, in which the images appear side by side, is usually brought about by involvement of the medial or lateral rectus muscles.

Orbital disease

The principal causes of restrictive ophthalmopathy are summarized in Table 13.11 (Fig. 13.6).

Thyroid ophthalmopathy

Thyroid ophthalmology (TO) is a common cause of proptosis with horizontal or vertical diplopia. It is associated with Grave's disease in >50% of patients and most of these patients are hyperthyroid at the time of diagnosis. There is conjunctival oedema, upper eyelid retraction, lid lag on down-gaze, poor eyelid closure due to proptosis and intraocular pressure may be elevated during attempted up-gaze. The most commonly affected muscles are inferior rectus, medial rectus and superior rectus with diplopia being worse in the direction opposing the involved muscle action. Therefore there is often limited elevation and abduction in one or both eyes with vertical misalignment. TO is caused by expansion of the extraocular muscles and orbital fat by an inflammatory infiltrate, mucopolysaccharide deposition and the subsequent development of fibrotic tissue (Fig. 13.7; Plate 13.24). The optic nerves may be compressed at the orbital apex by orbital congestion caused by swollen muscles and fat leading to visual failure. Choroidal folds or optic nerve swelling may be seen although fundal examination may be normal. Treatment of the endocrine disorder rarely affects the TO, ocular motility impairment may be

Table 13.11 Causes of restrictive ophthalmoplegia (progressive infiltration and fibrosis of extraocular muscles).

Dysthyroid eye disease	
Orbital pseudotumour (myositis)	
Primary or metastatic orbital tumours	Lymphoma
Other orbital masses	Paranasal sinus mucocoele
Intracranial masses extending into orbit	Sphenoid wing meningioma
Infiltration of extraocular muscles	Dysthyroid eye disease, sarcoidosis, amyloidosis, acromegaly, infection
Entrapment of extraocular muscle due to trauma	
Caroticocavernous fistula	

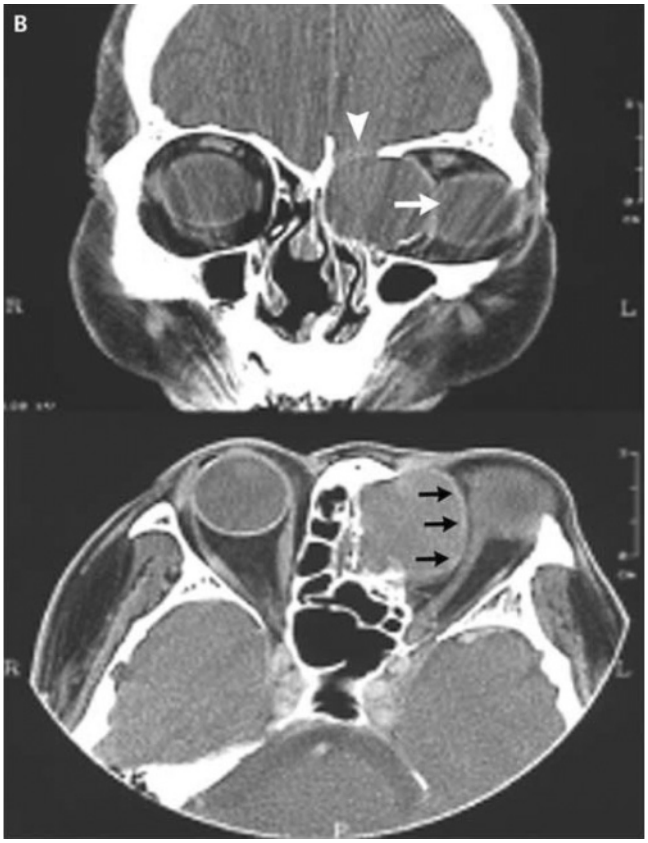

Figure 13.6 Ethmoid mucocoele causing visual impairment. A cystic lesion is seen in the left ethmoid sinus compressing the globe (black and white arrows) and eroding the lamina papyracea and part of the skull base (white arrowhead). (From Lee 2008, with permission.)

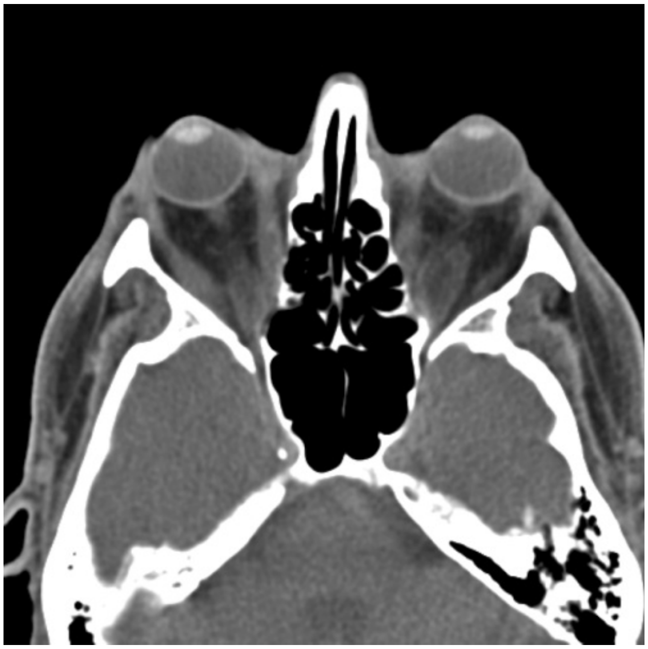

Figure 13.7 Extraocular muscle enlargement causing compressive optic neuropathy in thyroid eye disease.

treated surgically but optic neuropathy may require steroids or urgent surgical decompression.

Orbital inflammatory syndromes

Idiopathic inflammatory disorders may be classified according to their mode of onset, anatomical localization and physical signs or histopathological subtype. In particular they may be divided into orbital pseudotumour when the inflammation primarily involves the structures in and around the orbit (sclera, ocular muscles and lids) or the condition is often referred to as Tolosa–Hunt syndrome when the inflammation primarily involes the cavernous sinus, superior orbital fissure or orbital apex. In orbital inflammation the cellular component of the infiltrate is highly variable but includes mature T lymphocytes, plasma cells, macrophages, eosinophils and polymorpholeucocytes. Connective tissue may show oedema, fibrosis or sclerosis. Clinically, orbital inflammation is associated with localized ipsilateral pain, conjunctival injection, unilateral lid oedema and erythema, proptosis, ophthalmoplegia and a palpable orbital mass. Any lacrimal gland infiltration leads to enlargement.

In Tolosa–Hunt syndrome involvement of the superior orbital fissure is characterized by proptosis, ophthalmoplegia, trigeminal sensory loss and Horner's syndrome. Ophthalmoplegia without proptosis suggests cavernous sinus involvement.

Orbital myositis is often unilateral and occasionally only a single muscle is affected but any combination of extraocular muscles may be involved. Symptoms may be due to paresis or restriction but conjunctival injection and pain on eye movements are characteristic.

Imaging may be helpful with inflammation appearing as low signal in T1 and T2 weighted images with marked contrast enhancement. On CT the inflammatory tissue appears isodense with the extraocular muscles. The course of orbital inflammatory pseudotumour, orbital myositis and Tolosa–Hunt syndrome is usually one of prompt response to systemic steroids but then relapse as the steroids are reduced which may prompt the use of additional steroid-sparing agents such as azathioprine, methotrexate or mycophenolate mofetil.

Lymphoma is the most important differential diagnosis of the inflammatory orbital syndromes and if prompt response to steroids does not occur then a biopsy should be considered. Other primary and systemic syndromes must be considered in the differential diagnosis of orbital inflammatory syndromes. Inflammatory disease of the orbit may be infective, particularly in children when it is a medical emergency. In orbital cellulitis, ophthalmoplegia is associated with fever and lid swelling. Proptosis occurs with paranasal sinus or metastatic infection. Mucormycosis (Chapter 8) is an acute fungal infection which occurs in the immuno-compromised patient and is particularly associated with diabetic ketoacidosis, haematological malignancy and organ transplantation. Rhino-orbital cerebral mucormycosis develops by inhaling spores onto the oral and nasal mucosa following which direct invasion of the orbits occurs via the paranasal sinuses or the brain and via the sphenoid sinus, superior orbital fissure, cribriform plate or via the orbital vessels and nerves. The condition is characteristically unilateral with an acute onset of fever, headache, sinusitis, peri-orbital pain, cellulitis, rhinorrhoea and trigeminal anaesthesia. Ophthalmic involvement is a result of direct fungal infiltration or ischaemic infarction and this leads to acute ophthalmoplegia, proptosis, peri-orbital oedema and blindness from central retinal artery occlusion or an optic neuropathy. Mucormycosis may cause an orbital apex or cavernous sinus syndrome. Neurological involvement may lead to internal carotid artery occlusion, meningitis or cerebral abscess. Radiology shows mucosal thickening, orbital infiltration, bony destruction or ophthalmic vein thrombosis. However, tissue diagnosis is usually established by nasal biopsy demonstrating large branching hyphae which invade the vessels. Mucormycosis carries a high mortality rate and requires aggressive antifungal treatment and surgical debridement.

Inflammatory disease of the orbit may be caused by granulomatous disease (tuberculosis, sarcoidosis), systemic vasculitis (Wegener's granulomatosis) or neoplasm (lymphoma or metastasis). Metastatic cancer (particular breast) may spread to the orbit causing a bilateral inflammatory mass. Lymphoid neoplasm tends to develop at a later age, is often bilateral and is less characteristically associated with pain or ophthalmoplegia.

Cavernous sinus thrombosis

A number of conditions may lead to thrombosis within the cavernous sinus. Infectious causes may spread from local structures either directly or via vascular pathways, e.g. facial and dental infections, sinusitis, otitis media or orbital cellulitis. Underlying medical conditions that may predispose to cavernous sinus thrombosis include diabetes mellitus, malignancy and collagen vascular disease. There is usually peri-orbital pain with proptosis, chemosis, ptosis and ophthalmoplegia. Patients may present with headache, nausea and vomiting, occasionally encephalopathy and early involvement of the VIth nerve occurs before total ophthalmoplegia develops. With increasing venous stasis optic disc swelling may develop leading to optic neuropathy or retinal ischaemia. Meningitis or cerebral abscess is associated with extension beyond the cavernous sinus. The CSF may show meningitis and imaging confirms involvement of the cavernous sinus and superior ophthalmic vein. Other causes of lesions of the cavernous sinus are considered below.

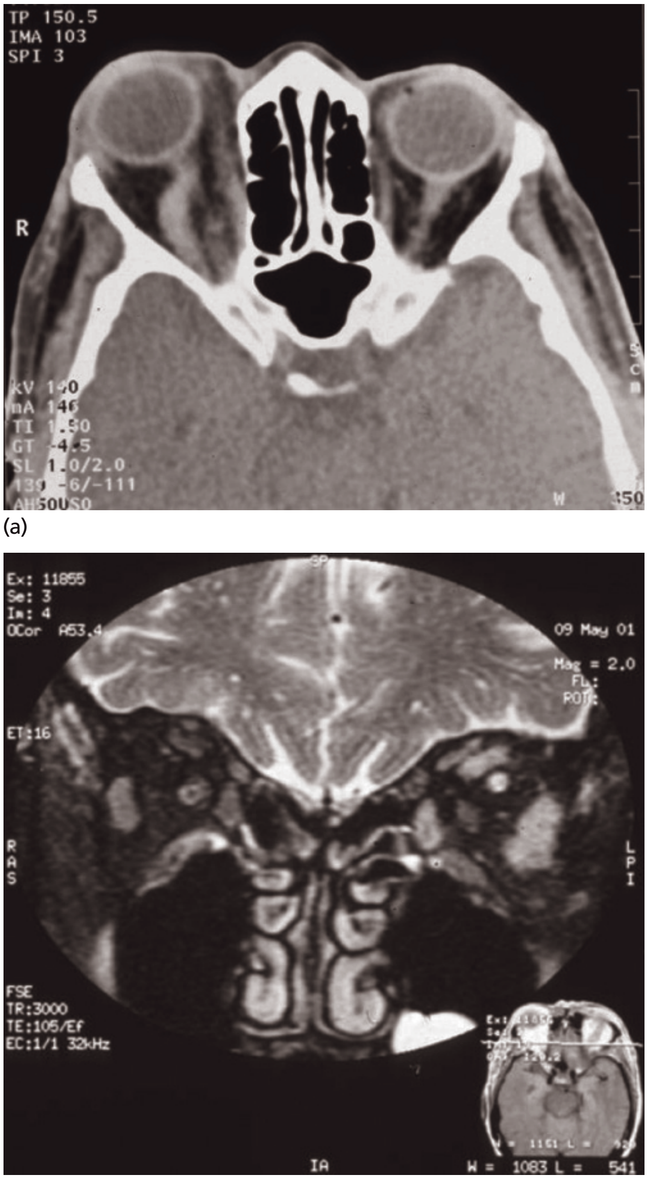

Figure 13.8 (a) Orbital computed tomography (CT) showing dilated right superior ophthalmic vein in carotid-cavernous fistula. (b) Coronal magnetic resonance image (MRI) showing enlarged extraocular muscles and high signal from superior ophthalmic vein in left carotid-cavernous fistula.

Carotico-cavernous fistula

Carotico-cavernous fistula (CCF) is an abnormal arteriovenous communication between the carotid artery and the cavernous sinus (Fig. 13.8; Plate 13.25). The fistula is considered direct if the arterial supply is derived from the internal carotid artery itself and indirect if the supply is via the extradural meningeal branches of the internal or external carotid artery. The fistula is indirect in >90% of cases and may be located anywhere along the course of the intracavernous carotid artery. It may project anteriorly or posteriorly. The most common cause of CCF is head trauma which may be either penetrating or non-penetrating and not necessarily associated with a fracture of the skull base. Other causes include rupture of an intracavernous aneurysm, systemic vasculopathy, Ehlers–Danlos syndrome or fibromuscular dysplasia. Direct CCF may present within a few days of trauma but indirect CCF may be delayed and manifest with mild signs such as red eye and subtle orbital congestion. If the blood escapes posteriorly through the superior and inferior petrosal sinuses, ocular signs may be minimal although an expanded inferior petrosal sinus will cause direct compression of the VIth cranial nerve. However, anterior flow of high pressure arterial blood into the orbital veins leads to raised episcleral venous pressure, reduced arterial perfusion pressure and venous stasis. Although the signs are usually ipsilateral, the contralateral eye may be involved because of the variable connections between the two cavernous sinuses.

In an anterior direct CCF there is pulsatile proptosis associated with chemosis, arterialization of the conjunctival vessels (Plate 13.26) and an orbital bruit. Ophthalmoplegia may be a result of compression of the cranial nerves within the cavernous sinus or direct muscle involvement with orbital hypoxia and oedema due to venous stasis. Visual loss occurs as a result of retinal ischaemia, ischaemic optic neuropathy, intracranial optic nerve compression or corneal ulceration. These effects result from a reduction in retinal blood flow, because of a drop in effective ophthalmic artery perfusion pressure, together with venous stasis caused by arterialization of the orbital venous circulation. Fundal examination shows features of a slow flow retinopathy with mild disc swelling, blot haemorrhages and micro-aneurysms, venous congestion and tortuosity. Central retinal vein occlusion, glaucoma, retinal detachment and vitreous haemorrhage may occur. The diagnosis is established on imaging by enlargement of the superior ophthalmic vein. Rapid diagnosis is essential because high intracranial venous pressure may cause venous haemorrhage. Transarterial balloon embolization is the most effective treatment.

Indirect CCFs are low-flow dural-based AVMs which are non-traumatic. Symptoms are often mild with conjunctival injection, mild ophthalmoplegia and elevated intraocular pressure or retinal vasculopathy which may threaten vision. Rarely, orbital

Table 13.12 Causes of progressive external ophthalmoplegia.

Mitochondrial myopathy – Kearns–Sayre
Myopathy
Congenital – central core, multicore, centronuclear, myotubular, nemaline
Congenital oculopharyngeal
Myotonic dystrophy
Neuromuscular junction
Myasthenia gravis
Botulism
Neurogenic disease
Abetalipoproteinaemia
Spinocerebellar ataxia

congestion may become severe if there is thrombosis of the superior ophthalmic vein. MRI may show distension of the cavernous sinus, of the superior ophthalmic vein and enlargement of the extraocular muscles. Angiography may be indicated.

Myopathy

Myopathy involving the extraocular muscles leads to progressive ophthalmoparesis termed chronic progressive external ophthalmoplegia (Table 13.12). This syndrome is brought about by a number of causes, each associated with limitation of eye movements and ptosis but normal pupillary function. Because of the slowly progressive and painless onset, patients are often asymptomatic. Oculocephalic and caloric stimulation do not increase the range of movements reflecting the infranuclear origin of the limitation and there is often symmetrical ptosis and moderate orbicularis oculi weakness.

Mitochondrial disease (Chapter 9)

Mitochondrial myopathy is an important cause of chronic progressive external ophthalmoplegia (CPEO) which may be an isolated finding in cases with mitochondrial or Mendelian autosomal recessive or dominant transmission. There may be an associated 'salt and pepper' retinopathy, as discussed above, or a symptomatic field constriction with bone spicules and disc pallor typical of retinitis pigmentosa. In Kearns–Sayre syndrome CPEO, ptosis and retinitis pigmentosa (developing before the age of 20) are associated with cardiac conduction deficit (heart block often requiring a pacemaker), cerebellar signs and a raised CSF protein. CPEO is also prominent in mitochondrial gastrointestinal encephalomyopathy. Muscle biopsy shows the presence of 'ragged red fibres' within a population of relatively normal fibres on modified Gomori trichrome staining representing degenerate mitochondria. Electron microscopy confirms abnormal morphology of the mitochondria. A deletion in the mitochondrial DNA can be detected in >90% of patients with Kearns–Sayre syndrome and in 50% with CPEO alone.

Oculopharyngeal dystrophy

This is an inherited dystrophy affecting extraocular and bulbar muscles which is usually transmitted in an autosomal dominant pattern but rarely may be recessive. Bulbar weakness, if prominent, leads to severe dysarthria and dysphagia, predominantly affecting liquids with marked nasal regurgitation. There is bilateral ptosis, progressive ophthalmoplegia and facial weakness with occasional involvement of the jaw muscles leading to difficulty chewing. Muscle biopsy shows characteristic vacuolar myopathy with tubules.

Other causes of myopathy affecting the extraocular muscles include abetalipoproteinaemia (Chapter 18) which is characterized by childhood onset of CPEO, retinopathy and chronic fatty diarrhoea. There is malabsorption, low serum cholesterol and complete absence of betalipoprotein.

Neuromuscular junction

Ocular myasthenia gravis has been discussed in Chapter 9. The ophthalmoparesis is variable and may mimic any abnormal eye movement. It often fluctuates with prominent fatigability and variable ptosis. Nystagmus of an abducting eye mimicking internuclear ophthalmoplegia may occur and can develop rarely in the absence of extraocular muscle limitation. Weakness of orbicularis oculi is usually associated. In long-standing ocular myasthenia there may be a severe fixed ophthalmoplegia with ptosis which may be difficult to distinguish from myopathy or mitochondrial disorder. Congenital myasthenia and Lambert–Eaton syndrome may affect the extraocular muscles.

Botulism (Chapter 8 and 19) is associated with external ophthalmoplegia and ptosis which may preceed the develop of dilated, poorly reactive pupils and paralysis of accommodation. The presence of associated gastrointestinal symptoms and muscarinic anticholinergic effects helps to distinguish botulism from myasthenia gravis.

Cranial nerve palsies

Oculomotor nerve (IIIrd nerve palsy)

The IIIrd nerve originates in several subnuclei in the dorsal midbrain (Table 13.13). The fascicle exits the brainstem ventrally in close relation to the red nucleus and corticospinal tract. It traverses the subarachnoid space and passes through the lateral wall of the cavernous sinus. Just before entering the orbit via the superior orbital fissure, it divides into a superior branch, which innervates the levator palpabrae superioris and the superior rectus, and an inferior branch which innervates the inferior and medial recti, the inferior oblique and the iris sphincter and ciliary muscle. In the subarachnoid space and cavernous sinus the pupillomotor fibres of the IIIrd nerve lie superficially and dorsally and are vulnerable to compression from above. The IIIrd nerve supplies the medial rectus, inferior oblique, inferior rectus and superior rectus muscles, the lid levator and the parasympathetic innervation of the pupillary sphincter and ciliary body. Patients with a IIIrd nerve palsy complain of binocular diplopia. With a complete lesion there is ptosis, a fixed dilated pupil and the eye is deviated 'downward and outward' with residual function only in abduction (lateral rectus) and intorsion (superior oblique). Elevation, depression and adduction of the eye are impaired. With partial lesions involvement of extraocular muscles is incomplete

Table 13.13 Causes of oculomotor (IIIrd nerve) palsy.

Nucleus	i/l III but with c/l superior rectus involved. Ptosis will be either bilateral or absent.	Infarction Haemorrhage Trauma Tumour Infection
Fascicular	Signs of midbrain impairment – c/l ataxia, cerebellar tremor, hemiparesis, choreiform movements	Infarction Haemorrhage Tumour Demyelination Syphilis Trauma
Subarachnoid space	Usually isolated May be headache or orbital pain	Aneurysm (PComm A, ICA, basilar, PCA) Ischaemic (microvascular) Tumour (meningioma, chordoma, pituitary, metastases, carcinomatous meningitis) Infectious (meningitis, syphilis, *Borrelia*, herpes zoster) Herniation Trauma
Tentorial edge	Uncal herniation	Raised intracranial pressure Idiopathic intracranial hypertension Hydrocephalus Trauma
Cavernous sinus and superior orbital fissure	IV, VI, VII, sympathetic fibres (Horner's syndrome). Ophthalmic division of V or its branches	Tumour (pituitary adenoma, meningioma, nasopharyngeal carcinoma, lymphoma, metastases) Inflammation (Tolosa–Hunt) Aneurysm – ICA, PComm Ischaemic (microvascular) Cavernous sinus thrombosis Dural carotico-cavernous fistula ICA stenosis/dissection
Orbital	Optic neuropathy, chemosis, conjunctival injection, proptosis	Trauma Tumour Inflammatory Infection (fungal) Dural arteriovenous malformation Sphenoid sinus mucocoele

c/l, contralateral; i/l, ipsilateral; ICA, internal carotid artery; PCA, posterior cerebral artery; Pcomm, posterior communicating artery.

and the pattern may resemble myopathic or restrictive disorders. In microvascular disease, the perforating vasae nervorum are primarily occluded affecting the central fibres and extraocular movements.

Two patterns of motility abnormalities are characteristic of lesions of the oculomotor complex: First, an isolated complete bilateral ptosis arising from lesions exclusively affecting the caudal part of the oculomotor nerve complex where the common cell group supplying both levator palpebrae superioris muscles lie. Secondly, a unilateral palsy of the medial rectus, inferior rectus and of inferior oblique together with a contralateral superior rectus palsy. This occurs when half of the oculomotor complex is damaged because most of the axons from the subnucleus of the superior rectus decussate to innervate the contralateral muscles.

Nuclear oculomotor palsies are usual vascular in origin. The upper midbrain is supplied by the posterior subthalamic paramedian branches of the P1 segment of the posterior cerebral artery (PCA) while the lower midbrain is supplied by three vascular territories: paramedian [IIIrd nerve nucleus and part of the medial longitudinal fasciculus (MLF)] supplied by direct twigs from the basilar artery; basal (IIIrd nerve fasciculus and brachium conjunctivum) supplied by the short circumferential branches of the superior cerebellar artery (SCA) and P1 branches of PCA; dorsolateral supplied by the long circumferential branches of SCA and P1 of the PCA. Oculomotor palsies are often associated with supranuclear eye movement disorders because of the close relationship to the supranuclear pathways and centres particularly if the cause is haemorrhagic, infiltrative or neoplastic.

Fascicular lesions. Lesions of the fascicle rarely occur in isolation but are usually associated with disorders of the brainstem which involve other nuclei and pathways. A number of characteristic syndromes are recognized. Involvement of other midbrain structures in the paramedian territory help to localize the lesion. In Claude's syndrome there is involvement of the superior cerebellar peduncle leading to a cerebellar tremor with contralateral ataxia. A variant of this condition is Nothnagel's syndrome in which involvement of the brachium conjunctivum leads to ipsilateral ataxia. In Weber's syndrome, involvement of the cerebral peduncle leads to a contralateral hemiparesis and in Benedikt's syndrome involvement of the red nucleus – substantia nigra leads to contralateral coarse tremor or choreiform movements. Less commonly, isolated fascicular lesions may cause pupil sparing IIIrd nerve palsy or isolated involvement of the superior or inferior divisions of the IIIrd nerve.

Subarachnoid space. Within the interpeduncular space the nerve passes beneath the origin of the PCA and lateral to the posterior communicating artery to run along the free edge of the tentorium and pierce the dura to enter the cavernous sinus lateral to the posterior clinoid body. It is vulnerable to ischaemia, meningeal processes including infection, inflammation, neoplasia and haemorrhage or to compression by arterial aneurysms.

Patients with ischaemic IIIrd nerve lesions present with preserved pupillary function because involvement of vasae nervorum leads to damage within the deep substance of the nerve but does not involve pupillomotor fibres which lie dorsal and peripherally in the nerve. However, microvascular IIIrd nerve palsy resulting from diabetes may cause some pupil involvement in a minority of cases. Compressive lesions of the IIIrd nerve in the subarachnoid space usually cause an ipsilateral fixed dilated pupil which is painful. The most common cause is an intracranial aneurysm arising at the junction of the posterior communicating and internal carotid arteries. Less commonly, the aneurysm may arise from the top of the basilar or the junction of the basilar and superior cerebellar arteries. The IIIrd nerve may become compressed against the tentorial edge, petrous ridge and clivus by the uncus of the temporal lobe during cerebral herniation. The pupillomotor fibres are usually involved first, leading to dilatation of the pupil. Traumatic lesions of the IIIrd nerve are rare and usually arise from severe head injury causing root avulsion at the brainstem origin or damage at the point of dural perforation or in the superior oblique fissure.

Within the cavernous sinus involvement of the oculomotor nerve is usually associated with lesions of other cranial nerves (IV, V and VI) and the oculosympathetic fibres. There is usually facial pain and the pupil may be mid-sized and poorly reactive. Compression may be caused by an aneurysm of the internal carotid artery, other causes are listed in Table 13.14.

Lesions of the orbit typically respect the bifurcation of the nerve or reflect individual muscle involvement. They are commonly associated with proptosis and optic neuropathy leading to visual loss.

Table 13.14 Causes of lesions of the oculomotor nerve in the cavernous sinus.

Tumours	Nasopharyngeal carcinoma, pituitary adenoma, plasmacytoma, lymphoma, Hodgkin's disease, haemangioma, meningioma, VIth nerve tumour, sphenoid sinus tumour, skull base tumour
Vascular	Cavernous sinus thrombosis, cavernous sinus fistula, superior ophthalmologic vein thrombosis Internal carotid artery – aneurysm, dissection, occlusion
Sphenoid sinus mucocoele	
Infection	Herpes zoster
Inflammatory	Tolosa–Hunt syndrome, vasculitis, Wegener's granulomatosis

Abberant reinnervation (oculomotor synkinesis) is relatively common following oculomotor nerve injury or prolonged compression as with meningioma or aneurysm. A number of characteristic patterns are seen. These include co-contraction of the levator and medial rectus on attempted adduction or co-contraction of levator and inferior rectus on attempted down-gaze and pupillary constriction on medial or downward eye movement.

Abducens nerve (VIth nerve palsy)

Abducens nerve palsy causes binocular horizontal diplopia due to ipsilateral rectus paresis with a primary position esotropia. The causes are summarized in Table 13.15.

The VIth nerve nucleus is located in the caudal paramedian pontine tegmentum beneath the floor of the IVth ventricle. The facial nerve loops around the nucleus and the MLF passes medially. The fascicle has a long intrapontine course and lesions are frequently associated with other neurological signs. It emerges from the brainstem ventrally and traverses the subarachnoid space in close relationship to the anterior inferior cerebellar artery. Within the cavernous sinus it lies free in the body unsupported by the sinus wall (unlike III and IV) before passing through the annular segment of the superior orbital fissure to innervate the lateral rectus muscle.

Nuclear lesions are commonly vascular and several characteristic syndromes of pontine infarction are recognized. Involvement of the anterior inferior cerebellar artery (Foville's syndrome) leads to a lesion of the pontine tegmentum which causes an ipsilateral gaze palsy because the abducens nucleus contains both abducens motor neurones and interneurones joining the MLF and ascending to the contralateral III nucleus. This is often associated with facial nerve palsy, loss of taste in the anterior two-thirds of the tongue, Horner's syndrome, analgesia of the face, peripheral deafness (VIIIth nerve) and contralateral loss of pain and temperature sensation over the trunk and limbs. Involvement of the ventral paramedian pons is associated with damage to the corticospinal tract leading to a contralateral hemiplegia (Raymond's syndrome) or the facial nerve fasciculus leading to facial palsy (Millard–Gubler syndrome).

Congenital paralysis of abduction is usually associated with syndromes of nuclear aplasia including Möbius' and Duane's syn-

Table 13.15 Causes of abducens (VIth nerve) palsy.

Nuclear	Horizontal gaze palsy (rostrolateral pons) c/l internuclear ophthalmoplegia	Möbius' syndrome Duane's syndrome Infection Tumour Demyelination Wernicke encephalopathy Trauma
Fascicular	i/l dysmetria, i/l Horner's, c/l internuclear ophthalmoplegia	Infection Demyelination Tumour Inflammation Wernicke–Korsakoff syndrome
Subarachnoid	i/l dysmetria, c/l hemiparesis	Aneurysm – ICA Subarachnoid haemorrhage Trauma Infections – meningitis, syphilis, *Borrelia*, TB, HIV Inflammatory – vasculitis, sarcoid, SLE, Wegener's granulomatosis Tumour – VI nerve, cerebellopontine angle, clivus, lymphoma, carcinomatous meningitis Raised intracranial pressure
Petrous apex	VI, VII, deafness. Facial pain	Infection of mastoid or tip of petrous bone Otitis media Gradenigo's syndrome Thrombosis of inferior petrous sinus or transverse/sigmoid sinus Trauma Downward displacement of brainstem by supratentorial mass Tumour – nasopharyngeal
Cavernous sinus and suiperior orbital fissure	III, IV, V_1 sympathetic	ICA aneurysm/dissection Cavernous sinus thrombosis Carotico-cavernous fistula Tumour (pituitary adenoma, nasopharyngeal carcinoma, meningioma) Sphenoid mucocoele Tolosa–Hunt syndrome Infection – VZV
Orbital	Ophthalmoplegia, proptosis, chemosis	Tumour Infiltration Infection Trauma

c/l, contralateral; i/l, ipsilateral; ICA, internal carotid artery; SLE, systemic lupus erythematosus; TB, tuberculosis; VZV, varicella zoster virus.

drome. Within the subarachnoid space the abducens nerve may be involved by meningeal inflammation and infiltration. However, a VIth nerve palsy is not localizing and it may be due to any cause of raised or reduced intracranial pressure including transtentorial herniation.

Lesions at the apex of the petrous are associated with facial palsy and involvement of V, VII and VIII cranial nerves. Tumours at the clivus such as nasopharyngeal carcinoma, meningioma and chordoma may cause bilateral VIth nerve lesions because the nerves lie close at this point. Within the cavernous sinus the VIth nerve is vulnerable because it is not tethered to the dural wall and may therefore may be involved by intracavernous vascular lesions but skull base or parasellar tumours may also be responsible. Lesions at the orbital apex are associated with proptosis and chemosis. In contrast to the oculomotor nerve, the VIth nerve is frequently involved by head trauma even if this is relatively mild.

Acute onset of painful VIth nerve palsy is often due to microvascular ischaemia. Bilateral VIth nerve palsies are associated with raised intracranial pressure, subarachnoid haemorrhage, meningitis, Wernicke's encephalopathy and tumours.

Trochlear nerve (IVth nerve palsy)

Trochlear nerve palsy causes binocular vertical diplopia with tilting of objects (torsional diplopia) which is worse on looking down and is caused by ipsilateral superior oblique weakness (Table 13.16). There is elevation of the affected eye with vertical diplopia and head tilt away from the side of the lesion.

The trochlear nerve originates in the dorsal midbrain. The fascicle passes laterally to the aqueduct and exits the midbrain dorsally. The nerves cross in the superior medullary velum before passing around the midbrain tectum to reach the free end of the tentorium and then pass forward into the wall of the cavernous sinus. The nerve enters the orbit through the superior orbital fissure and innervates the contralateral superior oblique muscle.

Congenital trochlear palsy is relatively common and may be caused by aplasia of the nucleus or a developmental anomaly of the superior oblique tendon in the orbit. The trochlear nerve is rarely involved by intrinsic brainstem lesions because of the short intramedullary course of its fascicle. Isolated trochlear nuclear lesions cause a contralateral superior oblique palsy. There is usually also a Horner's syndrome ipsilateral to the lesion because of the proximity of sympathetic fibres. Bilateral IVth nerve palsy may be due to a lesion in the superior medullary velum.

The most common cause of trochlear palsy is trauma, possibly because the tectum of the midbrain shifts as a result of contrecoup trauma and may compress the IVth nerve either in the superior medullary velum or against the tentorial notch. Microvascular ischaemic disease may also cause IVth nerve palsy. Other causes of IVth nerve palsy are summarized in Table 13.16.

Painful and combined ophthalmoplegia

Multiple ocular motor palsies are usually unilateral and result from lesions in the cavernous sinus or superior orbital fissure. The principal causes are summarized in Table 13.17.

Bilateral lesions suggest a diffuse disorder of muscle (see above), a neuromuscular abnormality (e.g. myasthenia gravis) or a neurogenic cause (e.g. Guillain–Barré syndrome, Fisher syndrome), diffuse infiltrative brainstem lesions, infection or neoplastic disease affecting the meninges. Painful combined ophthalmoplegia is usually due to inflammatory, neoplastic or vascular disease as discussed, other causes are summarized in Table 13.18.

Table 13.16 Causes of trochlear (IVth nerve) palsy.

Nuclear and fascicular	Aplasia Haemorrhage/infarction (mesencephalic) Tumour AVM Trauma Demyelination Neurosurgical complication
Subarachnoid	Trauma Tumour – pineal, tentorial meningioma, ependymoma, haemangioblastoma, metastases Aneurysm – superior cerebellar, PCA, PComm A Hydrocephalus Meningitis (infectious, neoplastic) Superficial siderosis Inflammatory – Wegener's granulomatosis
Cavernous sinus and superior orbital fissure	Tumour (pituitary adenoma, nasopharyngeal carcinoma, meningioma) Tolosa–Hunt syndrome Infection – VZV Carotid aneurysm/dissection Cavernous sinus thrombosis Carotico-cavernous fistula
Petrous	Infection of mastoid or tip of petrous bone Thrombosis of inferior petrous sinus Trauma Downward displacement of brainstem by supratentorial mass Aneurysm, AVM
Orbital	Trauma Tumour infiltration
Unknown	Microvascular infarction

AVM, arteriovenous malformation; PCA, posterior cerebral artery; PComm A, posterior communicating artery.

Table 13.17 Causes of unilateral multiple ocular motor nerve palsies.

Brainstem	Supranuclear signs i/l limb ataxia c/l involuntary movements c/l hemiparesis i/l VII	Haemorrhage/infarction Tumour Infection – encephalitis
Subarachnoid		Meningitis (infectious, neoplastic) Trauma Tumour – clivus Aneurysm – superior cerebellar, PCA, PComm A
Cavernous sinus and superior orbital fissure	III, IV, V_1, VI, VII, sympathetic fibres	Tumour [pituitary adenoma, nasopharyngeal carcinoma, meningioma, cavernous angioma, lymphoma, myeloma, lymphoma, Waldenström's, metastases (breast, lung, prostate)] Carotid aneurysm, occlusion/dissection Cavernous sinus thrombosis Carotico-cavernous fistula Cavernous sinus sepsis Tolosa–Hunt syndrome Infection – VZV
Orbital		Infection – fungal (mucormycosis) Trauma Tumour Aneurysm of ophthalmic artery
Localization uncertain		Guillain–Barré/Miller–Fisher syndrome Sjögren's syndrome

c/l, contralateral; i/l, ipsilateral; PCA, posterior cerebral artery; PComm A, posterior communicating artery; VZV, varicella zoster virus.

Table 13.18 Causes of painful ophthalmoplegia.

IIIrd nerve palsy due to aneurysmal compression	
Cavernous sinus disease	Thrombosis Intracavernous carotid aneurysm Inflammatory: Tolosa–Hunt Sarcoid Wegener's granulomatosis
ICA dissection	
Pituitary apoplexy	
Giant cell arteritis	
Nasopharyngeal carcinoma	
Basal meningitis	

ICA, internal carotid artery.

Central disorders of eye movements

Normal vision requires the ability to shift gaze rapidly to bring an object of attention into foveal vision (saccadic system) and a system to stabilize the new image on this area even if there is movement of the object (smooth pursuit and vergence) or of the head and body (vestibulo-ocular and opto-kinetic reflexes). The anatomical and physiological basis of these systems has been extensively reviewed in specialized texts (Brazis *et al*. 2001; Leigh & Zee 2006).

Supranuclear eye movement abnormalities result when the cerebral, cerebellar and brainstem afferent inputs to the ocular motor nuclear are disrupted.

Saccadic eye movements

The assessment of saccadic eye movements is discussed in Chapter 3. They are best examined by telling the patient to fixate alternately between two targets: saccades in each direction can be examined in each field of gaze in both horizontal and vertical planes. The examiner notes whether the saccades are of normal velocity, promptly initiated, accurate and conjugate.

Disorders of saccadic eye movements consist of abnormalities of velocity, accuracy, initiation, premature termination of gaze during saccades and the presence of saccadic intrusions and oscillations.

Velocity. Slow saccadic movements occur either in the direction of a paretic extraocular muscle or, if there is an internuclear ophthalmoplegia, in adduction. Slow saccades with a full range of movement occur in degenerative disorders affecting the parapontine reticular formation: spinocerebellar ataxia, Alzheimer's disease, Parkinson's disease and Huntington's disease. Slowing of vertical saccades is characteristic of progressive supranuclear palsy (PSP) while prolonged latency of saccadic movements is seen in corticobasal degeneration.

In myasthenia the initial velocity of the saccade may be abnormally fast with fatigue during the course of the movement.

Accuracy. Dysmetric (inaccurate) saccades are seen in cerebellar disorders, neurodegenerative conditions or as a consequence of drug toxicity (particularly anticonvulsants). In lesions of the cerebellar vermis and brachium conjunctivum, saccades may have an abnormally large amplitude (hypermetric) away from the side of the lesion. Saccadic hypermetria leads to macro-saccadic oscillation around the target. These oscillations may also be associated with hypometric saccades.

Initiation. Delayed initiation of saccadic movements and prolonged latency may be caused by lesions anywhere within the saccadic pathways, particularly frontal, collicular or pontine damage. Saccadic latency is increased in PSP and corticobasal degeneration. Ocular motor apraxia is characterized by loss of voluntary control of saccadic and pursuit eye movements with preservation of reflex movements, especially slow and quick phases of the vestibulo-ocular reflex. Patients have difficulty in making horizontal and vertical saccades to command although reflex and random saccades are normal. Ocular motor may be congenital but when acquired indicates bilateral hemispheric disease and is particularly associated with Balint's syndrome and cortical visual loss (see below). Abnormalities of saccadic initiation are also common in parkinsonian syndromes and progressive ataxia.

Impersistence and gaze distractability. Saccadic movements are often abnormal in neurodegenerative disease, particularly Alzheimer's, when large amplitude saccadic intrusions deviate the eyes away from the intended direction of gaze. There may also be a distractibility of gaze in which there is an inability to fix on a target while being distracted by an alternative peripheral target. On head turning there may be an ocular deviation with skew and the complete absence of saccadic movements. In neurodegenerative disorders period alternating gaze deviation with tonic deviation of the eyes and the head to one side may also occur followed by a slow deviation over 10–15 seconds to the other side.

Intrusions. Saccadic intrusions may take several forms. Square wave jerks occur during fixation when there is a conjugate displacement of the eye followed by a refixation saccade. These are seen in cerebellar disease and PSP but are also described in many other neurodegenerative disorders. High-amplitude macro-square wave jerks are seen in cerebellar disorders, multiple system atrophy and Chiari malformation. In ocular flutter, which occasionally occurs in MS, there are bursts of saccades with no intersaccadic interval. Opsoclonus (saccadomania) suggests brainstem (particularly pontine) disease. This is a multidirectional sequence of conjugate saccadic eye movements of large amplitude which persist during eye closure and sleep. It occurs as a paraneoplastic or post-infective phenomenon and may be associated with drug ingestion.

Horizontal gaze palsy

Horizontal gaze palsy refers to a restriction of conjugate eye movements that affect both eyes in a symmetrical manner. Unilateral restriction of horizontal voluntary gaze is usually due to a contralateral frontal or ipsilateral pontine lesion.

Frontal lobe lesions occur acutely as the result of a cerebrovascular event affecting ipsilateral horizontal smooth pursuit and causing a sustained ipsilateral horizontal gaze deviation with head rotation – the patient is said to be looking towards the side of the lesion and away from the hemiparesis. The gaze palsy can be overcome by oculo-cephalic stimulation and usually resolves over several days although residual impairment of saccadic and smooth pursuit persists. Frontal horizontal gaze palsy is usually due to an extensive vascular lesion often haemorrhagic involving the post-Rolandic cortex or subcortical fronto-parietal region and the internal capsule. Aversive eye deviation is associated with an epileptic focus but this often resolves rapidly.

Lesions of the posterior parietal cortex and temporo-occipital parietal region cause ipsilateral horizontal gaze preference and decrease the gain and maximum velocity of smooth pursuit eye movements towards the side of the lesion. Contralateral sensory and visual inattention may be associated.

Thalamic lesions cause abnormalities of horizontal and vertical gaze with conjugate deviation of the eyes away from the side of the lesion and towards the hemiparesis. Pontine lesions involving the paramedian pontine reticular formation (PPRF) or the VIth nerve nucleus lead to a horizontal gaze palsy with the eyes deviated away from the side of the lesion and an inability to move either eye beyond the midline towards the side of the lesion. The palsy may be incomplete. Oculo-cephalic stimulation by passive horizontal rotation of the head directly stimulates the VIth nerve but will not overcome the gaze palsy caused by pontine nuclear or infranuclear lesions. Horizontal gaze palsy in the pons may be a result of ischaemic, infarction, acute infection or inflammatory change, tumours or trauma.

Vertical gaze palsy

Vertical gaze palsy may be caused by lesions affecting the visual pathway from the cortex (frontal and parieto-occipital) to the vertical gaze centre in the rostral midbrain. Rarely, non-dominant hemispheric lesions may cause up-gaze palsies and thalamic lesions have also been associated with vertical gaze palsy.

Midbrain disorders most commonly result in disturbances of vertical eye movements that can be related to involvement of the posterior commissure, the rostral interstitial nucleus of the MLF (riMLF) or the interstitial nucleus of Cajal (iC). Lesions in the posterior commissure cause loss of up-gaze and Parinaud's syndrome (dorsal midbrain or pretectal syndrome) which includes lid retraction (Collier's sign) and occasionally ptosis, down-gaze preference, disturbance of vergence eye movements including convergence–retraction nystagmus, skew deviation and pupillary light near dissociation. The lesion is usually bilateral and Parinaud's syndrome is caused by tumours (pinealoma, glioma, metastases), obstructive hydrocephalus (dilation of the IIIrd ventricle and aqueduct) and by vascular occlusion (perforating branches of posterior cerebral artery) or thalamic and midbrain haemorrhage.

Up-gaze palsy resulting from lesions of the rostral midbrain nuclei is associated with hypersomnolence and impaired consciousness because there is involvement of the reticular activating system. There may be behavioural disturbances, associated with thalamic impairment, including amnesia, apathy, slowness of thought and akinetic mutism. This clinical pattern is seen as part of the 'top of the basilar syndrome'.

Bilateral defects in the riMLF result either in paralysis of down-gaze or loss of downward saccades. This is seen in a number of neurodegenerative or metabolic storage diseases including PSP, Niemann–Pick disease type C, Whipple's disease, Wilson's disease and Wernicke's syndrome. Combined loss of up-gaze and down-gaze for all eye movements suggests extensive bilateral rostral midbrain impairment involving riMLF and iC.

Oculogyric crises

Oculogyric crises are episodes of fixed conjugate upward (and occasionally lateral) deviation of the eyes first described in encephalitis lethargica. The crises are accompanied by behavioural disturbances including obsessive thoughts or depression and dystonic or dyskinetic limb movements. The episodes occur most commonly in association with metoclopramide or neuroleptic medication but are also described with other forms of brainstem encephalitis, parkinsonian syndromes or as a paraneoplastic phenomenon. The anatomical basis remains unknown.

Internuclear ophthalmoplegia

Internuclear ophthalmoplegia (INO) is caused by a lesion of the MLF which lies between the VIth nerve nucleus and the contralateral medial rectus oculomotor subnucleus. The abducens nerve and the MLF coordinate conjugate horizontal eye movements with co-contraction of the contralateral medial rectus and ipsilateral lateral rectus. If there is a lesion of the MLF the horizontal PPRF can communicate with the adjacent ipsilateral VIth but the other pathway to the contralateral IIIrd nerve nucleus is interrupted. This leads to impaired adduction (incomplete and decreased velocity) of the eye ipsilateral to the MLF lesion and ataxic nystagmus of the contralateral eye. The nystagmus may be the most prominent feature. Convergence is usually preserved because the IIIrd nerve and medial rectus continue to work normally if conjugate movements are not required. When INO is bilateral there is usually vertical nystagmus on up-gaze. INO is a characteristic sign of demyelination resulting from MS or other forms of inflammation but is also common in brainstem vascular disease. It is also seen in Wernicke's encephalopathy and can occur as a paraneoplastic sign.

One and a half syndrome

This is associated with a unilateral lesion of the dorsal pontine tegmentum affecting the ipsilateral PPRF, MLF and VIth nerve nucleus. There is dysconjugate horizontal gaze palsy and an internuclear ophthalmoplegia leading to complete impairment of horizontal gaze in the direction of the lesion and impaired adduction when looking in a contralateral direction. Vertical movements and convergence are spared. This condition is usually caused by a pontine infarct or MS although any structural lesion may be responsible.

Wall-eyed bilateral internuclear ophthalmoplegia (WEBINO)

This syndrome occurs if, in the presence of bilateral internuclear ophthalmoplegia, both eyes deviate laterally rather than remaining aligned in the primary position, convergence is often absent. This is caused by extensive lesions involving each MLF.

Internuclear ophthalmoplegia of abduction

This describes paresis of ipsilateral abduction occasionally associated with adducting nystagmus in the contralateral eye. This has been associated with ipsilateral rostral pontine and mesencephalic lesions. The paresis of abduction may be prenuclear and suggests an ipsilateral inhibitory correction between the PPRF and oculomotor nucleus.

Disconjugate vertical gaze palsy

A number of disconjugate vertical gaze palsies have been described. These include mononuclear elevator paresis in which the eyes are straight in the primary position of gaze but the affected eye will not elevate. Full elevation on eye lid closure confirms the supranuclear origin of the defect. It is associated with a lesion immediately rostral to the oculomotor nucleus. A vertical one and a half syndrome may also occur in association with vertical up-gaze palsy and monocular paresis of down-gaze associated with thalamo-mesencephalic infarction.

Skew deviation

Skew deviation is a vertical misalignment caused by an acquired supranuclear or vestibulo-ocular dysfunction. Hypertropia may be the same (concomitant) in all positions of gaze or may vary with eye position or alternate in left and right gaze. Non-concomitant skew deviation can mimic a single extraocular muscle paresis but there are usually accompanying brainstem signs. Skew deviation represents an imbalance in the otolith input because of a peripheral or central lesion. There is generally a downward and inward rotation of the eye on the side of the lesion and upward and outward rotation of the opposite side. Skew deviation is often associated with an INO. In some patients, skew deviation may be associated with ocular torsion which can be sustained (tonic or paroxysmal) and give rise to a compensatory head tilt – the ocular tilt reaction. Skew deviations are seen commonly in peripheral and central vestibular disease with intrinsic brainstem lesions and with cerebellar disorders.

Nystagmus

Horizontal nystagmus

Nystagmus is an involuntary rhythmic regular oscillatory movement in one or both eyes in any field of gaze. It usually consists of alternating phases of slow drift with a quick corrective fast 'jerk'

Table 13.19 Nystagmus in normal subjects.

Gaze evoked nystagmus
Endpoint nystagmus
Fatigue nystagmus
Optokinetic nystagmus
Vestibular nystagmus

Table 13.20 Types of nystagmus in children.

Congenital nystagmus	
Acquired nystagmus	Secondary to structural brain lesion
	Secondary to any condition causing reduced vision
	Monocular – optic glioma
	Spasmus nutans
	Nystagmus block syndrome

saccade in the opposite direction (jerk nystagmus). In some cases the movements have the same speed in both phases which is usually slow and sinusoidal (pendular nystagmus). Nystagmus reflects a disorder in the mechanisms that maintain steady gaze. Nystagmus occurring in the comatose and critically ill patient has been discussed in Chapter 19.

Nystagmus in normal subjects

Some normal subjects show endpoint gaze evoked nystagmus on extreme lateral or vertical gaze. This may be asymmetrical having a greater amplitude in the abducting eye but tends to wane after several seconds (Table 13.19). Optokinetic nystagmus (OKN) is a jerk nystagmus induced by moving repetitive visual stimuli across the visual field. It is composed of an initial slow pursuit eye movement and a compensatory fast saccadic movement that shifts the eyes back towards fixation. This is a physiological form of nystagmus and the amplitude in the two eyes is equal regardless of the direction in which the stimulus is moved. The optokinetic response is reduced in association with lesions of the deep parietal lobe. Reduced OKN amplitude of an affected eye in adduction is a valuable way of demonstrating an internuclear ophthalmoplegia. Normal OKN pattern is retained with functional visual loss.

Jerk nystagmus

Jerk nystagmus is characterized by an initial slow drift away from the fixation target followed by a fast correcting phase back towards the target. The abnormal slow phase is mediated by the smooth pursuit system and the fast phase by the saccadic system. It is the direction of the fast component that defines the direction of the nystagmus. The amplitude is normally increased on gaze in the direction of the fast component (Alexander's law). Nystagmus in the primary position is defined by its trajectory (i.e. horizontal, torsional, upbeat, downbeat or mixed) and by the direction of the fast phase.

Pendular nystagmus

In pendular nystagmus both phases of the oscillation are of equal velocity. The movement is usually vertical with a torsional component superimposed but may be horizontal, oblique or rotatory. It is usually present in the primary position and does not vary with gaze direction. The movements may fluctuate, be different in both eyes or may be monocular. Occasionally, saccadic or fast phases may be superimposed upon a pendular nystagmus. It may be congenital or acquired and cause severe oscillopsia which interferes with reading and is associated with impairment of visual acuity and visual blurring. Specific forms of pendular nystagmus include spasmus nutans, oculo-palatal myoclonus, see-saw nystagmus and oculo-masticatory myorhythmia (in Whipple's disease). Acquired pendular nystagmus is a rare and late manifestation of MS and it may also be associated with lesions in the pontine tegmentum particularly with brainstem stroke and encephalitis.

Nystagmus in childhood

Latent nystagmus in childhood is a congenital jerk nystagmus that only appears when one eye is covered (Table 13.20). It is a conjugate jerk nystagmus beating with the fast phase towards the fixating eye. When the other eye is covered, the nystagmus reverses its direction. Latent nystagmus may become manifest as oscillopsia in patients with strabismus, amblyopia or acquired visual loss who are only able to fix monocularly (manifest latent nystagmus).

Congenital nystagmus is noted at birth or in early infancy but may rarely emerge in teenage years or adulthood. The oscillations are generally horizontal and conjugate in all directions of gaze and are either pendular or a mix of jerk and pendular wave forms. The movements diminish with vergence and increase on attempted fixation. The amplitude can vary in different gaze positions but the direction of the nystagmus does not fluctuate. Some patients adopt a compensatory head turn to use the position with the lowest amplitude of ocular movement. Patients with congenital nystagmus show an inversion of OKN in which the quick phase is directed in the same direction as the drum is rotating. Congenital nystagmus is absent during sleep. It is usually idiopathic but may be associated with structural ocular lesions, retinal dystrophies or optic neuropathies. The nystagmus block syndrome refers to a form of conjugate horizontal congenital nystagmus that is absent or minimal when the fixating eye is in adduction but becomes more marked when it is in abduction.

Pendular nystagmus from visual loss

Vertical pendular nystagmus can result from any condition that causes visual loss in early childhood (Table 13.20). In adults, vertical pendular nystagmus may develop many years after visual loss. Nystagmus is usually low amplitude and low velocity and may resolve if vision is restored.

Spasmus nutans

This is a rare and benign syndrome that develops in infancy (<14 months) and resolves by 3 years. It is characterized by nystagmus, head nodding and abnormal head posture. The nystagmus is usually horizontal and pendular although it may be oblique. It is usually of low amplitude and high frequency and characteristically either monocular or markedly disconjugate. The head nodding usually appears first and disappears with sleep or changes in head position. The condition is often transient with good residual visual acuity although it can occasionally be associated with structural lesions causing impaired visual acuity.

Monocular nystagmus

This is often caused by spasmus nutans or uniocular visual loss from optic glioma. However, in practice it is more usually brought about by an asymmetrical congenital nystagmus.

Vestibular jerk nystagmus

This is caused by abnormalities in the peripheral or central vestibular system causing an imbalance in the mediation of the smooth pursuit eye movements. Diseases of the peripheral vestibular system involving the labyrinth or vestibular nerve result in a unidirectional horizontal or mixed horizontal jerk nystagmus with the fast phase directed away from the side of the lesion. The amplitude of the nystagmus increases as the eyes are turned in the direction of the fast phase. It is reduced by visual fixation and intensified by factors causing loss of visual fixation including the dark, wearing Frenzel goggles or by sudden changes in head position. Clinical correlates of peripheral labyrinthine disturbance include tinnitus, vertigo, deafness and falling in the direction of the lesion.

Gaze evoked or gaze paretic jerk nystagmus

Gaze evoked nystagmus is induced by holding gaze in an eccentric position. It is the most common form of nystagmus encountered in clinical practice. The eyes are unable to maintain the eye position and the orbital elastic tissue causes them to drift back into the primary position. This is followed by a corrective saccadic eye movement giving rise to the nystagmus. If an associated paresis of gaze is present, either because of a peripheral or central disturbance, the nystagmus is termed gaze paretic. Gaze evoked nystagmus is usually asymptomatic and is only rarely associated with oscillopsia or poor balance from gait ataxia. It is a relatively large amplitude nystagmus which beats in the direction of gaze and is associated with rebound nystagmus on return to primary position and impairment of horizontal smooth pursuit movements. An associated fatigue nystagmus may occur in normal subjects or in myasthenia gravis after extended maintenance of eccentric gaze. Gaze evoked nystagmus is associated with many medications including antiepileptic drugs, sedative and alcohol and may also be caused by structural lesions of the vestibulo-cerebellum or the brainstem.

Caloric nystagmus

Cold water instilled into the external auditory meatus results in a jerk nystagmus with the fast phase beating away from the irrigated side when the head is maintained at a 30° angle. Irrigation induces repetitive slow phases that are corrected by opposite directed saccadic quick phases. The presence of normal caloric nystagmus indicates that the brainstem vestibulo-ocular connections and the IIIrd and VIth cranial nerves are intact. Disturbances of caloric nystagmus have been discussed in more detail in Chapter 14.

Torsional nystagmus

This is usually caused by a brainstem lesion affecting the central projections from the anterior and posterior semicircular canals and the otolith, therefore interrupting the vestibular input to the ocular motor centres. Torsional nystagmus usually beats away from the side of a brainstem lesion and is a conjugate movement associated with oscillopsia. There is generally an associated skew deviation and impairment of smooth pursuit movements. There may also be an internuclear ophthalmoplegia and associated midbrain lesion affecting vertical gaze. Torsional nystagmus is usually caused by infarction of the brainstem but may be associated with MS, tumours or rhombencephalitis.

Central vestibular horizontal nystagmus

This is a low amplitude nystagmus in the primary position which is seen in patients with reduced pursuit movements because of large cerebral lesions. Lesions of the vestibular nuclei or cerebellar flocculus result in a variety of forms of nystagmus which may be bidirectional or purely vertical (upbeat or downbeat) but less commonly may be torsional or horizontal. Fixation does not reduce the amplitude and Frenzel goggles or darkness do not intensify the oscillations. Central vestibular nystagmus is usually associated with vascular lesions, MS or brainstem tumours. The fast phase of the nystagmus is directed towards the side of the lesion. Patients with cerebellopontine angle lesions may manifest both a gaze paretic nystagmus to the side of the lesion, as a result of a horizontal pontine gaze paresis, and a faster beating nystagmus in the opposite direction associated with vestibular involvement.

Vertical and other forms of nystagmus

Downbeat nystagmus

This is a jerk nystagmus in which there is a fast phase saccadic movement beating in a downward direction (Table 13.21). This occurs in the primary position and increases with downward and lateral gaze. It causes blurred vision, oscillopsia and gait imbalance. It is associated with lesions of the dorsal medulla leading to loss of tonic downward vestibular input causing the eyes to drift upwards or of the cerebellar flocculus which removes its tonic inhibition of upward vestibular eye movements. Downbeat nystagmus is therefore associated with gaze evoked and rebound nystagmus and abnormal smooth pursuit movements. Lower brainstem involvement may cause a coexisting internuclear ophthalmoplegia or skew deviation.

Downbeat nystagmus is particularly associated with lesions at the cervico-medullary junction (e.g. Arnold–Chiari malformation)

Table 13.21 Causes of downbeat nystagmus.

Craniocervical abnormalities	Arnold–Chiari malformation, basilar invagination, syringobulbia, Paget's disease, platybasia
Toxic – metabolic	Antiepileptic drugs lithium, alcohol (Wernicke's encephalopathy)
Cerebellar degeneration	Spinocerebellar atrophy, paraneoplastic, familial episodic ataxia, multiple system atrophy
Raised intracranial pressure	
Infarction	
Infection	
Demyelination (rare)	
Cerebellar tumour	
Head trauma	
Heat stroke	

Table 13.22 Causes of upbeat nystagmus.

Infarction	Medulla, cerebellum or superior cerebellar peduncle
Posterior fossa tumour	
Demyelination (common)	
Wernicke's encephalopathy	
Brainstem encephalitis	
Behçet's disease	
Meningitis	
Congenital	Leber's neuropathy
Toxins	Tobacco
	Antiepileptic drugs, ciclosporin
Paraneoplastic	

but is also seen in spino-cerebellar degeneration and in association with drug toxicity in particular antiepileptic drugs, lithium and alcohol.

Upbeat nystagmus

Upbeat nystagmus is a jerk nystagmus characterized by a slow downward drift and a saccadic correcting fast phase beating upward (Table 13.22). It is associated with midline lesions of the ponto-medullary or ponto-mesencephalic junctions causing loss of vestibular upward eye movement input. Oscillopsia is less frequent than with downbeat nystagmus and patients are either asymptomatic or complain of blurred vision. Upbeat nystagmus occurs in the primary position and increases with up-gaze. Impaired upward pursuit is seen and the condition is often associated with poor horizontal pursuit, gaze evoked nystagmus and rebound nystagmus. If the cause is a low brainstem lesion there may also be a skew deviation and an internuclear ophthalmoplegia. Upbeat nystagmus is caused by cerebellar degeneration, brainstem or cerebellar strokes and demyelination but may also occur with toxicity and Wernicke's encephalopathy.

Other forms of vertical eye movement disorders may be seen in states of impaired consciousness and are discussed in Chapter 19.

Nystagmus in oculopalatal tremor

This may be associated with an asymptomatic palatal tremor. More commonly, symptomatic palatal tremor follows brainstem infarction or cerebellar degeneration. The nystagmus is usually a slow vertical regular pendular movement, synchronous with the palatal movement. Oculopalatal tremor is associated with brainstem involvement and is often seen with a horizontal gaze or lower cranial nerve palsy, cerebellar dysarthria or damage to the spinothalamic tract. It is associated with lesions of the dentato-rubro-olivary region (Mollaret's triangle) which lead to denervation of the inferior olive which appears hypertrophied on MRI scan.

See-saw nystagmus

In see-saw nystagmus there is alternating elevation and intorsion of one eye while the opposite eye falls and extorts. Both components of the movements are pendular and they occur in rapidly alternating sequence. It is usually present in all positions of gaze but maximal in down-gaze. This form of nystagmus is associated with bitemporal hemianopia usually from a large suprasellar mass such as a craniopharyngioma or pituitary adenoma. The lesion often causes expansion of the IIIrd ventricle. It is also associated with vascular disease, particularly affecting the rostral mesencephalon.

Oculomasticatory myorhythmia

Oculomasticatory myorhythmia is a continuous slow rhythmic convergent–divergent nystagmus (i.e. the eyes oscillate horizontally towards and away from each other). There are synchronous diffuse muscle contractions particularly involving masticatory or facial muscles and occasionally the palate and mouth. This form of nystagmus is associated with Whipple's disease and occurs in about 20% of patients. There is often also a supranuclear gaze palsy affecting vertical and then horizontal eye movements with eventual loss of all eye movements.

Periodic alternating nystagmus

Periodic alternating nystagmus may occur as a congenital or acquired manifestation; it is a spontaneous horizontal jerk nystagmus that is present in primary position of gaze. It is present in one direction for around 120 seconds, it then stops for 5–20 seconds before beating in the other direction for a similar duration. In the interval between direction change, there may be a vertical nystagmus or square wave jerks. The horizontal nystagmus is least when looking in the direction of the slow phase. A complete cycle takes approximately 4 minutes and therefore may be missed on routine clinical examination. Periodic alternating nystagmus may be congenital or acquired in association with impairment of the vestibular cerebellar pathways. It is particularly seen with Arnold–Chiari malformation or cerebellar degeneration but may also be associated with MS or brainstem tumours.

Convergence-retraction nystagmus in Parinaud syndrome

This is characterized by rapid convergence movements of both eyes which also retract in the globe. It is best seen on attempted up-gaze or with a downward moving optokinetic drum and is caused by co-contraction of the horizontal recti on attempted convergence or up-gaze. Patients may have difficulty with upward saccadic movements but vertical pursuit is intact. It occurs with pupillary light-near dissociation and bilateral lid retraction and is associated with lesions of the dorsal rostral midbrain which involve the posterior commissure (e.g. pineal tumours).

Voluntary nystagmus

Normal individuals may be able to perform high-frequency horizontal conjugate eye movements which appear to be pendular. Occasionally they are vertical or circumrotatory. The movements tend to fatigue after more than a few seconds.

Eye lid nystagmus

Eye lid twitches may occur in synchrony with vertical nystagmus and may also be provoked by convergence. Similar eye lid twitches are seen with the fast phase of horizontal nystagmus on lateral gaze. Rarely, lid nystagmus may occur in isolation and it is particularly associated with medullary disorders. Irregular lid flutter may also be seen with weakness of up-gaze or in parkinsonism.

Chiasmal and retrochiasmal visual pathways

Chiasmal disease

At the optic chiasm the nerve fibres from the temporal retina (nasal visual field) maintain their relative position in the lateral chiasm before passing into the ipsilateral optic tract while the nerve fibres from the nasal retina (temporal visual field) decussate in the chiasm and pass into the contralateral optic tract. The separation of the two hemifields occurs at the fovea so that the visual field is split at the point of fixation into the right and left halves, thus the macular fibres are both crossed and uncrossed in the optic chiasm. Bitemporal hemianopia is the characteristic clinical sign of chiasmal disease.

In some individuals the intracranial portion of the optic nerve is relatively long and the chiasm is formed in the posterior cistern (post-fixed) with the consequence that expanding sellar lesions may cause compression of the optic nerve and anterior aspect of the chiasm. Lesions of the anterior chiasm can result in a contralateral temporal hemianopic field defect with an ipsilateral central scotoma. This is referred to as a junctional field defect. A central scotoma with a temporal hemianopic scotoma in the same eye is also a junctional pattern but is less often identified.

Conversely, the chiasm may be pre-fixed so that mass lesions of the pituitary fossa may impinge on the posterior aspect of the chiasm or optic tract. Lesions of the posterior chiasmal notch may selectively involve only dorsal crossing fibres which predominantly serve central vision thus resulting in a bitemporal hemianopic scotoma. However, macular fibres, which form at least 30% of all fibres despite serving only 5° of field, are present throughout the chiasm and therefore any form of chiasmal lesion usually causes a defect in central vision (e.g. acuity or colour vision) in one or both eyes as part of the bitemporal field loss.

Patients with bitemporal hemianopia may present with double vision despite normal eye movements. When there are dense temporal field defects, binocular fusion is not supported by overlapping temporal hemifields in the visual cortex. As a result, latent phorias may readily break down leading to variable vertical or horizontal diplopia. In other instances there may be difficulty in performing tasks requiring depth perception and judgement. The phenomenon of post-fixational blindness occurs when the subject with a bitemporal hemianopia fixates on a near target, causing objects beyond the target to project on to both nasal hemiretina and therefore be invisible. In chiasmal disorders, diplopia may also be caused by direct cranial nerve involvement, either because of compression or direct invasion of the cavernous sinus or as a consequence of raised intracranial pressure.

The characteristic appearance of the optic disc in pure bitemporal hemianopia is ‘band’ or ‘bow-tie’ atrophy. This occurs because exclusively crossing fibres enter the disc at the nasal and temporal poles. At all other locations there is a mixture of crossing and non-crossing fibres. Hence, if only crossing fibres are lost a ‘band’ of total atrophy which is rarely seen in a complete form except in chiasmal transection caused by trauma (Plate 13.27).

The causes of chiasmal compression and the management of lesions in the pituitary region is described in Chapter 20.

Homonymous hemianopia

Homonymous hemianopia is caused by unilateral lesions of the visual pathway posterior to the optic chiasm (i.e. optic tract, lateral geniculate body (LGB), optic radiation and cerebral cortex). Clinically, these are often disabling causing difficulty with reading and visual scanning. Patients may fail to notice relevant objects or obstacles on the affected side causing collisions with approaching people or cars. Transient homonymous hemianopia may occur in migraine, transient ischaemic attacks or seizures. The most common cause is vascular but homonymous hemianopia may result from tumours, trauma or surgery.

Optic tract

Each optic tract contains crossed and uncrossed nerve fibres subserving the contralateral visual field, in particular nasal fibres subserving the temporal visual field of the contralateral eye and ipsilateral temporal fibres subserving the nasal visual field. Therefore, the left optic tract contains fibres carrying information for the right half of the visual field from both the right and left eyes. Lesions of the optic tract cause homonymous visual field defects of the contralateral visual field. The optic tract lies in close proximity to the internal capsule, cerebral peduncle and basal ganglia. Optic tract lesions are rare and are usually associated with other visual system abnormalities. Tract lesions typically occur with suprasellar lesions (craniopharyngiomas, aneurysm, optic chiasmal glioma and rarely, pituitary tumours) which extend posteriorly especially when there is a pre-fixed chiasm.

Involvement of the optic tract may lead to a homonymous hemianopia which may be complete or incomplete. When incomplete the visual field loss is often non-congruent. Optic atrophy occurs in a ‘bow-tie’ distribution (band atrophy) in the eye with the temporal hemianopia because the fibres at the temporal poles of the disc are exclusively crossing fibres (Plate 13.27), where fibres crossing from temporal hemifields to enter the disc at both lateral poles are preferentially lost. A contralateral relative afferent pupillary defect may be present because the temporal hemifield served by the nasal hemiretina carries a greater number of ganglion cells that drive the light reflex than does the nasal hemifield. Lesions of the optic tract may be associated with hypothalamic involvement and contralateral hemiparesis from internal capsular damage.

Lateral geniculate body (LGB)

Most of the nerve fibres of the optic tract (>80%) project to the ipsilateral lateral geniculate nucleus in the midbrain. Other optic tract fibres innervate the Edinger–Westphal nucleus in the pretectum, providing the afferent limb of the pupillary light reflex. The axons from the ipsilateral eye terminate in the second, third and fifth laminae of the lateral geniculate body while the axons from the contralateral eye terminate in the first, fourth and sixth laminae. The nerve fibres are believed to form a precise retinotopic map of the LGB.

Lesions of the LGB are extremely uncommon and are caused by occlusive vascular disease involving the dual supply from the posterior cerebral and inferior choroidal arteries. Such lesions are associated with contralateral hemiparesis from involvement of the adjacent posterior limb of the internal capsule or contralateral hemisensory loss from thalamic involvement.

Horizontal bands of the ganglion may be destroyed resulting in a specific hemianopic wedge field defect (geniculate hemianopia) that straddles the horizontal meridian although congruous or non-congruous hemianopia are more common. The wedge-shaped defects are located near the horizontal meridian either involving or sparing fixation. Pupillary reactions are normal. There may be associated signs resulting from involvement of the ipsilateral thalamus and/or pyramidal tract.

Optic radiation

The neurones originating from the LGB form the optic radiation or the geniculo-calcarine tract and end in the primary visual cortex in the occipital lobe. The first part of the optic radiation is associated with the posterior limb of the internal capsule and lies in close proximity to the corticospinal and corticobulbar tracts as well as the thalamus and cortical fibres. Lesions of the optic radiation in this region typically produce contralateral and usually complete homonymous hemianopia associated with contralateral hemianaesthesia and hemiplegia. Relative afferent pupillary defects may occur in lesions that are close to the lateral geniculate body.

The inferior fibres that subserve the superior visual field initially course anteriorly, superior to and around the temporal horn of the lateral ventricle. They then pass laterally and posterior to the striate cortex forming Meyer's loop. It is believed that as these fibres approach the occipital cortex their retinotopic order increases and the left and right eye fibres representing common visual loci separate into ocular dominance columns in the striate cortex. Lesions of the optic radiation in the temporal lobe usually result in a congruous homonymous hemianopia primarily affecting the superior quadrant with preserved visual acuity and pupillary light reflexes. The defect may be incomplete, incongruous and either confined to the superior quadrants ('pie in the sky') or more dense superiorly than inferiorly. This field defect is associated with aphasia, memory deficits and visual hallucinations. It is caused by intrinsic tumours such as gliomas, metastases or large demyelinating plaques rather more frequently than vascular occlusion.

More dorsal fibres pass through the parietal lobe. Lesions of the optic radiation in this region lead to incomplete or mildly incongruous homonymous hemianopia which is either limited to the inferior visual field or is more dense inferiorly than superiorly. However, more extensive lesions may produce a complete homonymous hemianopia with macular splitting, preservation of visual acuity and normal pupillary reflexes. There may be associated disruption of optokinetic nystagmus. Contralateral hemifield neglect is also seen in lesions of the non-dominant parietal lobe and may be difficult to distinguish from a visual field defect. There can be an associated sensory defect and lesions extending into the dominant angular gyrus produce Gerstmann's syndrome (finger agnosia, agraphia, acalculia, right–left disorientation).

Visual cortex

The anatomical structure of the visual cortex and the associated striate and extrastriate cortex has been discussed in Chapter 2. The primary visual cortex (V1, calcarine cortex, striate cortex, Brodmann area 17) is believed to be retinotopically organized, based on visual information from the corresponding retinal loci from the two eyes. The posterior pole of the occipital lobe is concerned with the central visual field while the peripheral visual field is represented in the most anterior part of the striate cortex. The upper lip of the calcarine cortex receives projections from the inferior visual field. The striate cortex is surrounded by the visual association areas (V2–6, Brodmann areas 18 and 19). These areas are also believed to be retinotopically arranged with over-representation for the central visual field as in the primary visual cortex.

Various specific patterns of acquired field defect occur with lesions of the primary visual cortex. Occipital lobe lesions are the most common cause of homonymous hemianopia and are usually a result of infarction in the distribution of the posterior cerebral artery. Other aetiologies include venous infarction, haemorrhagic arteriovenous malformations and fistulas, tumours, abscess and trauma.

The most peripheral 30% of temporal field viewed by both eyes is not overlapped by corresponding nasal fields in the other eye (temporal crescent). This portion of the field therefore has a monocular representation in the anterior part of the contralateral visual cortex. Lesions of the anterior striate cortex cause a congruous homonymous scotoma with unilateral loss of the temporal crescent. This is the only example of a monocular visual field defect caused by a retrochiasmal lesion although a uniocular temporal scotoma is much more commonly caused by a peripheral retinal lesion. More commonly, when the anterior portion of the visual cortex is spared by an occipital lobe lesion, there is a complete homonymous hemianopia except for sparing of the temporal crescent in the contralateral eye.

Superior and inferior homonymous visual field defects respecting the vertical and sometimes the horizontal meridians occur with lesions of the occipital cortex selectively damaging either the inferior or superior banks (usually infarcts).

Lesions of the posterior half of the occipital region often cause homonymous hemianopia that spare the central macular 5–25° of visual field. This may be because there is a dual blood supply to the occipital pole (branches of the middle and posterior cerebral arteries), therefore occlusive or thromboembolic stroke affecting a single vessel will not cause infarction in macular cortex. Macula sparing has also been suggested to occur either because the macula is bilaterally represented in the occipital cortex or because there may be incomplete damage to the striate cortex on the affected side; however, these explanations cannot be supported experimentally. The precise explanation for macular sparing remains controversial as sparing only extends 10° into the blind hemifield but >60% of the visual cortex supplies this part of the visual field and much of this does not carry a dual blood supply. Furthermore, it is important to emphasize that macular sparing may not be clinically meaningful and cannot be easily diagnosed on visual testing because of wandering fixation.

Conversely, homonymous visual field defects preferentially involving the macular may occur. These respect the vertical meridian and are limited to the central 30° and are usually enclosed within an area of normal peripheral visual field. The cause is most commonly occipital tip injury resulting from hypotension or ischaemic stroke. However, larger lesions involving the occipital radiations and optic tract have also been associated with this deficit.

Bilateral homonymous hemianopia

This may occur with bilateral lesions of the occipital cortex either simultaneously or consecutively. The extent of the visual field defect depends on the involvement of the striate cortex. Bilateral occipital cortex lesions are relatively frequent because the two posterior cerebral arteries are terminal branches of a single basilar artery and therefore basilar occlusion will cause occipital infarction and cortical blindness. This may also occur in metabolic, neurodegenerative or inflammatory disease. A variety of bilateral homonymous lesions may occur ranging from complete bilateral homonymous hemianopia (cortical blindness), to bilateral macular sparing hemianopia (ring scotoma), quadrantanopias or scotomatous and altitudinal defects.

Anton's syndrome is particularly associated with occipital cortex lesions extending to the calcarine cortex and including visual association cortices (Brodmann areas 18 and 19). Acute bilateral and extensive lesions of the occipital lobe lead to sudden visual loss. Patients with cortical blindness appear to be unaware of their visual loss, deny any difficulty and confabulate about what they are able to see often being able to direct their gaze to auditory stimuli.

Blindsight and stato-kinetic dissociation

Blindsight or residual vision in an apparently blind hemifield (V1 scotoma) remains controversial. There is evidence that reflex motor responses may be generated in response to stimuli in the blind field. The underlying substrate for this is uncertain but is likely to involve subcortical visual pathway, the pulvinar of the thalamus and callosal connections. There is also a direct projection from the LGB to area 5, which may subserve preserved perception of movement. The Riddoch phenomenon of stato-kinetic dissociation may be demonstrated on Goldmann perimetry when a stimulus is perceived on movement in the periphery of a homonymous hemianopia despite failure to see colour or static forms.

Visual association areas (extrastriate cortex areas V2–6)

Lesions affecting the human area V1 often extend into underlying white matter in the prestriate area and adjacent parietal and temporal regions causing an inferior quadrantic field defect which respects the horizontal as well the vertical meridian. The prestriate pathways or visual association areas can be considered as two separate systems: first, a ventro-mesial pathway which occupies the occipital lobe below the calcarine fissure and adjacent temporal lobes and, secondly, a dorso-lateral area which is located in the occipital lobe above the calcarine fissue and in the adjacent parietal and temporo-parietal region. The clinical significance of this is that there may be functional partitioning of the pre-striate cortex in such a way that focal lesions may result in selective impairment of aspects of higher visual function.

Lesions of the ventro-mesial pathway in the occipito-temporal cortex result in defects of object recognition colour vision and reading affecting the contralateral hemifield. These include cerebral dyschromatopsia, pure alexia and prosopagnosia (see below) (Fig. 13.9). Hemianopic field defects are commonly found, often

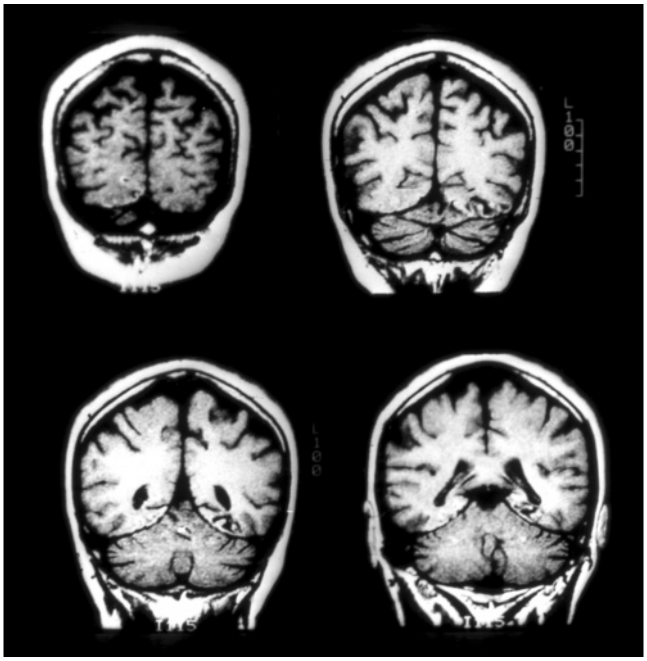

Figure 13.9 T1 weighted magnetic resonance image (MRI) showing bilateral ventral occipito-temporal infarction. The patient had prosopagnosia and cerebral achromatopsia.

bilateral inferior quadrantanopia as a result of damage to the adjacent ventral portion of the optic radiation. Lesions of the dorso-lateral pathway may cause Balint's syndrome, visual agnosia and cerebral akinetopsia (see below).

Disorders of higher visual function

Visual hallucinations

Visual hallucinations are formed or unformed images perceived when in reality there is no stimulus present and are the result of endogenous neural activity. Illusions are the misperception or distortion of a stimulus present in the external environment.

Visual hallucinations may occur in psychiatric, medical, neurological or ocular disorders. Simple visual hallucinations may consist of single discrete or flickering flashes of light (phosphenes or photopsia) which may result from lesions of the retina, choroid or optic nerve. There may be lines of different colours in the form of simple patterns (circles, fortification or zig-zag patterns) which may be associated with a defect in the field of vision and usually caused by migraine or occipital epilepsy. Simple visual hallucinations include brief vertical flashes of light (Moore's lightning streaks) which predominantly occur in the temporal field in association with eye movements and are associated with vitreous detachment. Spontaneous flashes precipitated by eye movement or loud unexpected sounds may be a manifestation of demyelination or other causes of optic neuropathy.

Migraine is the most common cause of visual hallucination and illusion. The disturbances may vary from elementary, predominantly black and white, visual disturbances, elementary positive (phosphenes or geometrical forms) or negative (scotomas) disturbances with more complex visual hallucinations and illusions. In particular, fortification spectra (teichopsia), scintillating lights and lines or zig-zag waves may occur and frank distortions including geometric forms, micropsia, macropsia and metamorphopsia. These may also occur in migraine without headache.

Visual hallucinations are particularly associated with simple and complex seizures arising in the occipital lobe with or without secondary generalization (Plate 13.28). These seizures may be associated with multiple types of hallucinations or illusions. In contrast to migraine, the hallucinations are usually brief, stereotyped and fragmentary and are usually multicoloured and occasionally complex with circular or spherical patterns. They are generally seen in the contralateral temporal field but may begin centrally. They may be prolonged in non-convulsive status and are sometimes perceived as unreal and associated with anxiety and an affective disturbance. It may be difficult to distinguish from migraine because a migraine-like headache may occur after an occipital lobe seizure, usually coming on several minutes after the hallucinations have stopped. Occipital and temporal lobe epilepsy may also be associated with distortions, particularly changes in size both micropsia and macropsia.

In transient visual loss caused by occipital ischaemia there may be coloured bright flashes (scintillations). Occipital lobe tumours may give rise to uniform visual hallucinations in one hemifield often associated with exercise, which are probably ictal in origin. Visual hallucinations may occur with posterior cerebral infarction involving the occipital lobe and thalamus (Plate 13.29).

Complex visual hallucinations are usually related to temporal lobe dysfunction. They may involve hallucinations of colour, face, texture and objects and correlate with cerebral activity in the ventral extrastriate visual cortex and their content reflects the functional specialization of the particular region of occipital cortex affected.

Hallucinations and illusions occur in a variety of other neurological disorders (Chapter 7). They are frequently seen in delirium from any cause when they are associated with an alteration in attention, concentration and the level of consciousness with disrupted sleep–wake cycle and agitation. The symptoms characteristically fluctuate. In diffuse Lewy body disease there are characteristically vivid visual hallucinations and similar phenomena may also be seen in Parkinson's disease particularly in the older and more cognitively impaired patient taking dopamine agonists. These hallucinations are often colourful, complex, involving scenes of people and animals. There may also be associated paranoid delusional disturbances. Visual hallucinations are less commonly seen in Alzheimer's disease, Pick's disease, Huntington's chorea and vascular dementia. Hypnogogic and hypnopompic hallucinations lasting several minutes are associated with narcolepsy. These are often colourful vivid images involving people, animals or landscape scenes and may be difficult to separate from reality.

Visual hallucinations associated with impaired vision (Charles Bonnet syndrome)

In patients with impaired visual acuity from a variety of primary ophthalmological disorders, particularly in the elderly, recurrent vivid hallucinations may occur despite normal cognition and insight. They may be more likely to occur in low light and are seen in the blind portion of the visual field. They are not stereotyped and often consist of vivid scenes which are predominantly coloured and often involve animals, flowers and people which are sometimes said to have a cartoon-like appearance. They may have normal proportion or be altered in size and may change shape when the subject reaches out to them. They can usually be stopped by opening and closing the eyes or by rapid eye movements. The patient invariably realizes that the hallucinations are unreal.

This syndrome may result from lesions throughout the visual pathway but is particularly associated with age-related degenerative retinal or neurological disease and is considered to be a release phenomenon of the ventral occipito-temporal cortex.

Peduncular hallucinosis

This occurs with lesions of the thalamus and upper midbrain (usually bilateral). These are vivid and usually well-formed colourful hallucinations or people, animals or complex scenes. There may be illusionary micropsia and the scenes are often considered to be pleasant. The hallucinations can last for minutes to

Table 13.23 Visual illusions in patients with partial visual loss.

Tessellopsia	Regular repeating patterns
Dendropsia	Branching patterns
Hyperchromatopsia	Hyperintense brilliant colours
Polyopia	Seeing a single target as multiple
Macropsia	Seeing objects enlarged
Micropsia	Seeing objects reduced in size
Metamorphopsia	Seeing distortion of perceived objects
Palinopsia	Persistence or recurrence of the visual image despite removal of the object
Allesthenia	Transportation of an object seen in a visual field to the contralateral visual field
Oscillopsia	Illusion of movement of the environment

hours and usually occur in the evening. There may be associated auditory and tactile hallucinations but insight is well preserved.

Other visual illusions may be experienced by patients with partial visual loss (Table 13.23).

Polyopia

Polyopia, in which a single target is seen as multiple, is a rare manifestation of lesions of the occipital cortex or central visual pathway and occurs with monocular viewing. The number of objects seen may vary from two to hundreds. The true image is seen and the false images are similar but tend to reduce in intensity, colour and size. Polyopia tends to develop several seconds after fixation and does not resolve with a pin-hole.

Palinopsia

Palinopsia is also associated with occipital or occipito-temporal disease and may occur as an ictal phenomenon. The image tends to recur immediately after the object has been removed or the gaze has been diverted, it is usually without colour and remains despite eye closure. Palinopsia may develop during recovery from cortical blindness and is particularly associated with non-dominant focal occipito-parietal lesions. It also occurs in association with a variety of medications, drug withdrawal and neurodegenerative disorders.

Other disorders of visual perception

Pulfrich phenomenon

Pulfrich phenomenon is caused by a difference in the latency of transmission in the optic nerve between the two eyes. This usually occurs because of the delay in conduction associated with demyelination or compression of the optic nerve. This leads to a loss of stereoscopic depth perception causing objects to cross the midline.

Hemifield slide

Bitemporal hemifield slide is caused by loss of overlapping regions of the binocular visual field. This may cause a disturbance to reading because there is a vertical break in horizontal lines of text. Similarly, a left homonymous hemianopia may impair the transition from the end of line of text to a new line on the left-hand side of the page. Patients with right parietal lobe lesions may neglect reading the left side of lines on a page.

Tilt

Environmental tilt is particularly seen following lateral medullary infarction. The tilt in the field of vision may be 90° or 180° and come on abruptly. Severe tilts tend to be brief in duration while smaller deviations may persist for longer periods.

Visual synaesthesia

Visual synaesthesia occurs when auditory, tactile or gustatory stimuli produce visual images and is associated with illusions throughout the visual pathway. Visual dysaesthesia occur when various unpleasant visual sensations are experienced when looking towards a blind field. They are often associated with lesions of the optic radiation.

Visual agnosia

Visual agnosia refers to an inability to recognize objects visually despite preservation of visual acuity, intellectual function, attention and language abilities. However, object recognition deficits may also occur as a result of visual form imperception despite normal acuity. These patients are unable to detect differences in object matching tasks. This may occur as a consequence of bilateral ischaemic lesions in the calcarine cortex. True visual object agnosia may occur at the level of perceptual analysis (apperceptive agnosia) or at the level of semantic analysis (associative agnosia). Apperceptive agnosia is observed in patients with lesions of the right posterior cortex and associative agnosia with left occipito-temporal lesions. Apperceptive agnosia is frequently associated with spatial impairments and associative agnosia with acquired dyslexia and colour agnosia.

Prosopagnosia

Prosopagnosia is a circumscribed form of visual agnosia in which there is failure to recognize previously familiar faces or to learn the appearance of new faces. This is a severe deficit and patients rely on individual facial features (e.g. glasses, beard or hairstyle) or non-visual clues (e.g. voice) to recognize others. However, some patients are able to judge age, gender and emotional expression. Prosopagnosia can be congenital or is associated with bilateral lesions particularly affecting the fusiform or lingual gyri and may occur in unilateral right hemisphere lesions and usually occurs with multiple deficits of cognitive function (Fig. 13.9).

Disorders of colour vision

Inability to recognize colours as a consequence of cortical deficits, occurs in several different clinical patterns. In cerebral achromatopsia patients are not able to read Ishihara plates or sort colours according to hue. There is complete loss of colour vision with colours appearing as shades of grey. This is associated with bilateral lesions or involvement of the non-dominant occipito-temporal lobe and there is usually a superior quadrantic field loss with involvement of the inferior striate cortex or optic radiations. There is often accompanying visual agnosia.

Prosopagnosia

Lesser forms of cortical colour agnosia is an inability to name colours or point to a colour named by the examiner while the patient is still able to read Ishihara plates or sort colours according to hue. This form of colour agnosia is associated with dominant hemisphere lesions involving the infero-medial aspect of the occipito-temporal area (Figure 13.9).

Cerebral metamorphopsia

Patients notice distortion of images which may be caused by spatial remapping around homonymous scotomas in which case it can be mapped in a predictable fashion. In other instances the distortions are bizarre, often frightening and specific to faces and hands (Plate 13.30).

Visual simultanagnosia

This syndrome may occur in isolation or in association with cortical visual loss. There is an inability to understand the visual field as a whole while individual elemental parts are attended and recognized. If the patient is presented with several figures he/she is able to recognize them individually but sees only one when they are presented in a group. Formal testing is difficult because patients use only macular vision and fail to keep their eyes focused on the target. The syndrome appears to be associated with an inability to sustain visuo-spatial attention. It is particularly associated with the visual field defects involving unilateral or bilateral inferior quadrantic field and may occur as a sequelae of posterior circulation watershed infarction in Balint's syndrome.

Cortical visual impairment

Balint's syndrome is characterized by the following:

1 *Ocular motor apraxia*: an inability to shift gaze on command due to difficulty initiating voluntary saccades to redirect attention to visual targets despite an unrestricted range of eye movements.

2 *Optic ataxia*: a disturbance of hand movements while reaching for a target under visual control. It is manifest as clumsiness of movement of the hand performed under visual guidance. This is present throughout the range of movement in contrast to cerebellar ataxia.

3 *Reduced visual attention manifest as simultanagnosia* (see above): there may also be a reduction in visual attention with functional constriction in the fields and altitudinal neglect.

Balint's syndrome is associated with bilateral posterior watershed lesions in the convexity of the hemispheres. It is also associated with Gerstmann's syndrome although the strength of associations with these defects as a syndrome remains open to question.

Occipital cortical visual disturbances may also occur as a consequence of posterior presentation of Alzheimer's disease which tends to come on at a young age with relatively preserved visual acuity and colour appreciation. There is often language defect with difficulty reading and marked visuo-spatial difficulties. MRI scan shows prominent occipito-parietal atrophy.

Alexia

This is the loss of reading ability in previously literate subjects. This may be caused by disturbance in language function but can also occur because of disruption of the visual pathways in the occipito-temporal area of the left hemisphere. In this situation pure alexia occurs without agraphia and therefore patients are able to write but cannot read what they have previously written despite adequate visual and language abilities. Alexia with agraphia is associated with Gerstmann's syndrome from lesions of the left angular gyrus and occasionally adjoining temporo- parietal junction and is associated with acalculia, right–left disorientation and finger agnosia.

Abnormalities of the pupil

The pupil is abnormal in a number of ocular as well as neurological disorders; only the latter will be considered in this chapter. The importance of pupillary change is not so much the fact that they cause serious symptoms (they usually do not), but that they may indicate serious underlying neurological disease.

A knowledge of the anatomy of the direct and indirect light reflexes and of the sympathetic supply are important in understanding pupillary change (Chapter 2), and abnormalities of pupillary function can be very helpful in localizing neurological disorders.

The size of the pupil is determined by the balance between parasympathetic (tending to constriction of the pupils) and sympathetic (tending to dilatation of the pupils). The size of the pupils is affected by the ambient lighting and many other factors including the level of alertness and emotional factors. Sometimes the pupils are naturally of slightly unequal size without any underlying pathology (physiological anisocoria).

The light reflex is mediated by afferent (optic nerve) and efferent (parasympathetic) fibres. The anatomy of these is discussed in Chapter 2.

Pupillary abnormalities in neurological practice are best considered in two categories:

1 Disorders of the light reflex;

2 Disorders of the sympathetic innervation to the eye.

Physiological anisocoria – clearly perceptible inequality of pupillary size – is present in 20% of the population. It varies from day to day and can even switch eyes. Its physiological nature can be confirmed by the observations that the measured inequality is similar in light and dark, and by the fact that the direct and indirect light reflexes are quite normal.

Disorders of the light reflex

These can be divided into afferent, central and efferent disorders. The afferent limb of the light reflex is via the optic nerve where fibres pass to the pretectal region and thence to the Edinger–Westphal nucleus bilaterally. The parasympathetic efferent outflow, firing of which causes constriction of the pupil, originates in the Edinger–Westphal nucleus. The preganglionic fibres follow the course of the IIIrd nerve to the ciliary ganglion and then synapse with the short post-ganglionic fibre which travels to the iris.

Complete afferent pupillary defect

When there is complete blindness because of a lesion in the anterior visual pathway of the eye, the ipsilateral and contralateral pupil will show no reaction on testing of the direct light reflex, but the indirect reflex in the blind eye will be normal (i.e. the pupil will constrict when light is shone into the opposite eye). This situation is encountered in any complete optic nerve lesion, and the most common causes are tumour or trauma.

The light reflex tests the integrity of the anterior visual pathways. A preserved light reflex, in the presence of apparent total blindness in the eye, indicates either that the blindness is feigned or that it arises from the posterior visual pathways.

Relative afferent pupillary defect

A pupil with a relative afferent defect (sometimes known as the Marcus Gunn pupil) is identified by the swinging light test. When light is directed into the affected eye this will cause mild constriction of both pupils (because of decreased response to light from the afferent defect), and when directed to the unaffected eye it will cause a normal constriction of both pupils (because of an intact afferent path in both the affected and unaffected eye). When the light is rapidly alternated between the two eyes, the normal reaction in the good eye will override the poorer reaction in the affected eye. Thus, when the pupil reactions are compared, the pupils in the affected eye react less well to the direct light source and in a severe case the pupil in the affected eye actually dilates when the light is swung on to that eye.

The presence of a relative afferent pupilary defect indicates that there is an abnormality in the afferent optic pathway to the eye – caused by unilateral (or at least asymmetrical) optic nerve disease (usually) or retinal disease. It is extremely rare for preretinal diseases to cause this sign provided the torch light is bright enough, nor will a 'lazy eye' or maculopathy cause this effect unless very extensive.

The most common optic nerve disorders causing a relative afferent papillary defect is optic neuritis associated with MS. Other causes include an ischaemic optic neuropathy, optic nerve tumour (optic nerve meningioma, glioma), orbital disease causing compression of the optic nerve (including thyroid orbitopathy), infection and inflammation including sarcoidosis and Lyme disease, radiation damage or trauma. Other unilateral optic neuropathies including LHON will also result in this sign.

Extensive retinal disease will sometimes cause a 'Marcus Gunn' effect. This may be seen with retinal ischaemia and detachment, macular degeneration, intraocular tumour and retinal infection but in these patients additional optic nerve disease must be excluded.

Central (midbrain) lesions of the light reflex

When the pupil is affected by a midbrain lesion, there are two common patterns: the Parinaud syndrome and the Argyll Robertson syndrome.

Argyll Robertson syndrome

This venerable sign is rarely encountered in clinical practice now. However, it used to be a common finding, characteristically in tertiary syphilis. The pupils typically are small and irregular and do not react to light but do react to accommodation (light-near dissociation). The features are caused by damage of the central inhibitory fibres ventral to the aqueduct. Similar pupillary abnormalities are occasionally encountered in diabetes, MS or myotonic dystrophy. Occasionally, the 'inverse Argyll Robertson pupil' (no accommodation reflex but a present light reflex) is observed in cases of tertiary syphilis and was common in encephalitis lethargica.

Parinaud syndrome

The Parinaud syndrome (synonym: dorsal midbrain syndrome) is a term used to describe a cluster of four clinical signs:

1 Dilated (or mid-dilated) pupils that do not react to light, but which do react to accommodation;
2 Paralysis of voluntary up-gaze with preservation of down-gaze, but with up-gaze preserved on the doll's head manoeuvre (a supranuclear gaze palsy);
3 Convergence retraction nystagmus on attempted up-gaze. The eyes pull inward on gaze and the eyeballs retract;
4 Eyelid retraction (Collier's sign).

Other ocular motor abnormalities may also be present.

The syndrome is caused by damage of fibres in the dorsal midbrain, specifically to the posterior commissure, the nucleus of the IIIrd nerve and the Edinger–Westphal nucleus. The syndrome can result from many pathologies in this anatomical location. It is a characteristic sign of a pineal gland tumour (usually a pinealoma). Other brain tumours in the same region can cause the same syndrome. MS, acute hydrocephalus, angiomas, infection (e.g. toxoplasmosis) and ischaemic or haemorrhagic stroke are uncommon causes. Transient Parinaud syndrome may rarely result from a tonic–clonic seizure.

Treatment is primarily directed towards aetiology of the dorsal midbrain damage. MRI is the common first choice investigation and will usually reveal the cause.

If the cause is alleviated, the eye findings of Parinaud syndrome generally improve, either rapidly or over a period of months. If symptomatic therapy is needed (which is rare) up-gaze palsy and the retraction nystagmus can be improved by bilateral inferior rectus recession.

Efferent parasympathetic defects of the light reflex

Anatomically these can be divided into preganglionic and postganglionic parasympathetic lesions. In acute preganglionic block, there is a large unreactive pupil with absent light and accommodation reflexes. If in isolation, it is usually a result of drugs or eye drops. One other common cause is the Holmes–Adie syndrome. Preganglionic lesions are usually associated with a IIIrd nerve palsy, it is often due to an acute compressive (neurosurgical) cause or basal meningitis. Other causes, and the clinical features, of IIIrd nerve palsy are considered above.

Holmes–Adie syndrome

This syndrome was named after William John Adie (1886–1935) and Sir Gordon Morgan Holmes (1876–1965), two Queen Square physicians. The Holmes–Adie syndrome is characterized by the occurrence of a 'tonic pupil'. The tonic pupil shows sectorial denervation of the sphincter pupillae and only portions of it react to light. The response to near is present but abnormally prolonged (hence 'tonic'). The syndrome is associated with the absence of deep tendon reflexes (sometimes complete absence or with preservation of some reflexes). It typically occurs in young adults (third to fifth decade), with a female preponderance. Often the second eye will be affected weeks or months later and initially preserved reflexes will then become absent. Once present, the condition persists. Some individuals with the Holmes–Adie syndrome also develop excessive sweating, sometimes unilaterally (Ross's syndrome). The Holmes–Adie syndrome is usually 'idiopathic' and benign, signifying no serious pathology. However, occasionally it can be associated with cardiovascular abnormalities or inflammatory conditions such as Sjögren's syndrome. It may rarely be familial.

The condition is often noticed by chance, when the affected individual looks in a mirror. Sometimes there is blurring of vision, photophobia (intolerance to bright light) because of pupillary dilatation, or difficulty with near vision because of failure of accommodation of the lens.

The cause is unknown but it is thought to be due to damage to the ciliary ganglion and the spinal ganglion. The diagnosis is made on clinical grounds. Treatment is not usually needed, but pilocarpine drops can be used, three times a day, to constrict the pupil if necessary. Thoracic sympathectomy or botulinum toxin injection is a definitive treatment for excessive sweating.

Disorders of the sympathetic nervous supply to the pupil

The sympathetic pathway originates in the posterior hypothalamas, travels through the brainstem (including the lateral medulla) and then descends in the cervical cord to the C8–T1 level. There the first order neurones synapse with the second order neurones which leave the cord and enter the paravertebral sympathetic chain to the superior cervical ganglion. They subsequently synapse with the third order (post-ganglionic fibres) which ascend around the internal carotid artery to the base of the skull. In the cavernous sinus they form a peri-arterial plexus in the adventitia of the artery. The ocular fibres pass through the superior orbital fissure in the long ciliary nerves while sudomotor and vasomotor fibres pass to the face via the external carotid artery. Excitatory fibres supply the dilator pupillae, Müller's muscle and the blood vessels of the eye. Inhibitory fibres supply the ciliary muscle and the sphincter pupillae.

Horner's syndrome

In 1869, the Swiss ophthalmologist Johann Freidrich Horner described this syndrome which is caused by dysfunction of the sympathetic nervous supply to the pupil. It can be caused by damage anywhere along the lengthy three-neurone sympathetic pathway – and can be divided into 'preganglionic lesions' (lesions of the first and second order neurones) and 'post-ganglionic lesions' (lesions of the third order neurones). It is an important syndrome, not because it affects vision itself (this is unusual) but because some of the common causes of the syndrome require urgent attention.

Clinical features

The cardinal signs are ptosis (from loss of sympathetic tone in Müller muscle) and miosis (constricted pupil). Other signs include upside-down ptosis (slight elevation of the lower lid), enophthalmos, conjunctival injection and anhidrosis (decreased sweating). If the syndrome develops in children, heterochromia may occur from lack of melanocyte action induced by the lack of sympathetic stimulation. An important clinical point is that the ptosis caused by Horner's syndrome occurs with a constricted pupil and the ptosis caused by a IIIrd nerve palsy is usually more severe and associated with a dilated pupil (from a loss of innervation to the sphincter pupillae).

Causes

Horner's syndrome can be congenital but is usually acquired. A list of causes is shown in Table 13.24.

Traumatic birth injury is one cause of a congenital Horner's (Klumpke paralysis) and the diagnosis is usually obvious. Most cases are isolated and idiopathic. Rare genetic causes also result in a congenital Horner's syndrome. Congenital cases show heterochromia (the affected iris is less pigmented).

The acquired causes are almost all unilateral, and can be caused by interference with the sympathetic nervous supply at any point in its long anatomical course (Chapter 2). A bilateral Horner's syndrome is characteristic of autonomic neuropathies (e.g. diabetes or amyloid). In children, the development of a Horner's syndrome requires urgent imaging to exclude a neuroblastoma. In adults, a characteristic presentation of dissection of the carotid artery is the development of a Horner's syndrome with ipsilateral neck or face pain. The Raeder syndrome (paratrigeminal syndrome) comprises oculo-sympathetic palsy and ipsilateral facial pain, often with some involvement of the trigeminal and oculomotor nerves. Pancoast tumour, carcinoma at the apex of the lung, also may present

Table 13.24 Acquired causes of unilateral Horner's syndrome.

Type of lesion	Anatomical position	Common pathologies
Preganglionic		
First order neurone	Hypothalamus, midbrain, pons, medulla, cervical cord	Multiple sclerosis Tumour Vascular lesion (in medulla, as part of the lateral medullary syndrome; Wallenberg's syndrome) Syringomyelia
Second order neurone	T1 level of spinal cord/column, sympathetic chain, the superior cervical ganglion	Thoracic cord lesions Neck trauma Spinal column lesions and disc prolapse Cervical rib Aneurysm/dissection of aorta or subclavian artery Central venous catheterization Abscess or infection, lymphadenopathy Thyroid neoplasm Lesions in the apex of the lung (especially Pancoast's tumour)
Post-ganglionic		
Third order neurone	Internal carotid artery, base of the skull, ophthalmic nerve, cavernous sinus, superior orbital fissure, orbit	Aneurysms or dissection of the internal carotid artery Cavernous sinus lesion (fistula, aneurysm, granuloma) Skull base or orbital tumour Skull base malformation (e.g. Arnold–Chiari malformation) Infection Meningioma Trauma Nasopharyngeal carcinoma Orbital pathology (including trauma, tumour, granuloma, infection) Neuroblastoma (in children) Herpes zoster

Table 13.25 Summary of responses to topical agents in Horner's syndrome. (From Bremner 1999, with permission.)

	1% phenylephrine	4% cocaine	1% hydroxyamphetamine
Normal	No response	Dilates	Dilates
Preganglionic Horner's syndrome (recent)	Sometimes dilates	No response	Dilates
Preganglionic Horner's syndrome (long-standing)	Sometimes dilates	No response	No response
Post-ganglionic Horner's syndrome	Sometimes dilates	No response	No response

with a Horner's syndrome. Cluster headaches cause a transient Horner's syndrome, which is useful in diagnosis.

Diagnosis

The clinical features are so characteristic that no diagnostic tests are usually needed. However, the diagnosis of the underlying cause depends on the clinical situation and will often involve imaging, including MRI and MR angiography.

Pharmacological tests can be used to confirm the diagnosis and to differentiate a preganglionic from a post-ganglionic Horner's syndrome. The most reliable test for confirmation of the diagnosis is instillation of 4% cocaine on to the pupil. This prevents re-uptake of noradrenaline in the sympathetic nerves to the iris dilator muscles and causes dilatation. In a Horner's syndrome, no such dilatation occurs. The instillation of 1% hydroxyamphetamine and phenylephrine will help differentiation a post-ganglionic and preganglionic Horner's syndrome (Table 13.25).

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14

Neuro-Otology: Problems of Dizziness, Balance and Hearing

Rosalyn Davies, Linda Luxon, Doris-Eva Bamiou, Simon Shorvon

Dizziness and vertigo: introduction

Dizziness is an umbrella term describing symptoms varying from vague light-headedness to disorientation, disequilibrium or vertigo. Vertigo means the illusion of movement of either the body or the surroundings, typically spinning or sometimes tilting or rocking to and fro.

Vertigo, this illusion of movement is either of internal origin – a mismatch between sensory inputs, or it may be linked to retinal slip during the slow phase of nystagmus, i.e. the image moves across the retina; in each case the surroundings or the head seem to move. Much information can be gleaned from detailed descriptions of dizziness and especially vertigo, sometimes pointing to the specific semicircular canal involved. Any vestibular dysfunction can be accompanied by:

- Vertigo – rotary, swaying, tilting or postural imbalance;
- Blurring of vision or slippage of the visual field with head movement; and
- Autonomic symptoms – nausea, vomiting, sweating, distress and anxiety.

Severe acute vertigo causes prostration and exceptionally, brief loss of consciousness.

Epidemiology

Dizziness and vertigo is common. One UK community survey showed that 1 in 4 adults have had significant dizziness. Dizziness is a substantial cause of morbidity, loss of time from work, repeated medical attendances and costly investigation – one study showed that on average more than four physicians were visited before precise diagnosis of a vestibular problem. Dizziness is a frequent reason for consultation by those over 65 years and, like headache, is common worldwide.

Basic concepts

Three-dimensional spatial orientation

Balance is achieved and maintained by a complex sensorimotor system. Orienting sensory information is derived from the paired vestibular labyrinths, visual input and somato-sensory afferents (joint, tendon and muscle position sense, and superficial sensation). This information converges on the brainstem vestibular nuclei to be integrated with modulating influences from the reticular activating system and higher centres: cortex, cerebellum and extrapyramidal system. Effector pathways from the vestibular nuclei project to the oculomotor nuclei (eye movement), i.e. the efferent limb of the vestibulo-ocular reflex, a three neurone reflex arc. Other efferents pass to the neck, trunk and limb muscles, part of the vestibulo-spinal tracts, that modulate spinal reflex arcs. Efferents also project to the vestibular cortex from the brainstem (Fig. 14.1).

The vestibular system has three primary functions:

1 To stabilize gaze in space during head movement, e.g. reading a sign while walking;

2 To control posture when the head and body are static, e.g. while standing, during self-motion and during passive motion; and

3 To facilitate perception of orientation and motion.

Vestibulo-ocular reflexes

The parallel vestibular and oculomotor systems have evolved so that they function in three similar planes (Fig. 14.2). These planes of head movement are:

- *Yaw*: head rotation about the vertical *z*-axis;
- *Pitch*: head flexion/extension about the horizontal *y*-axis; and
- *Roll*: lateral head tilt about the horizontal *x*-axis.

Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

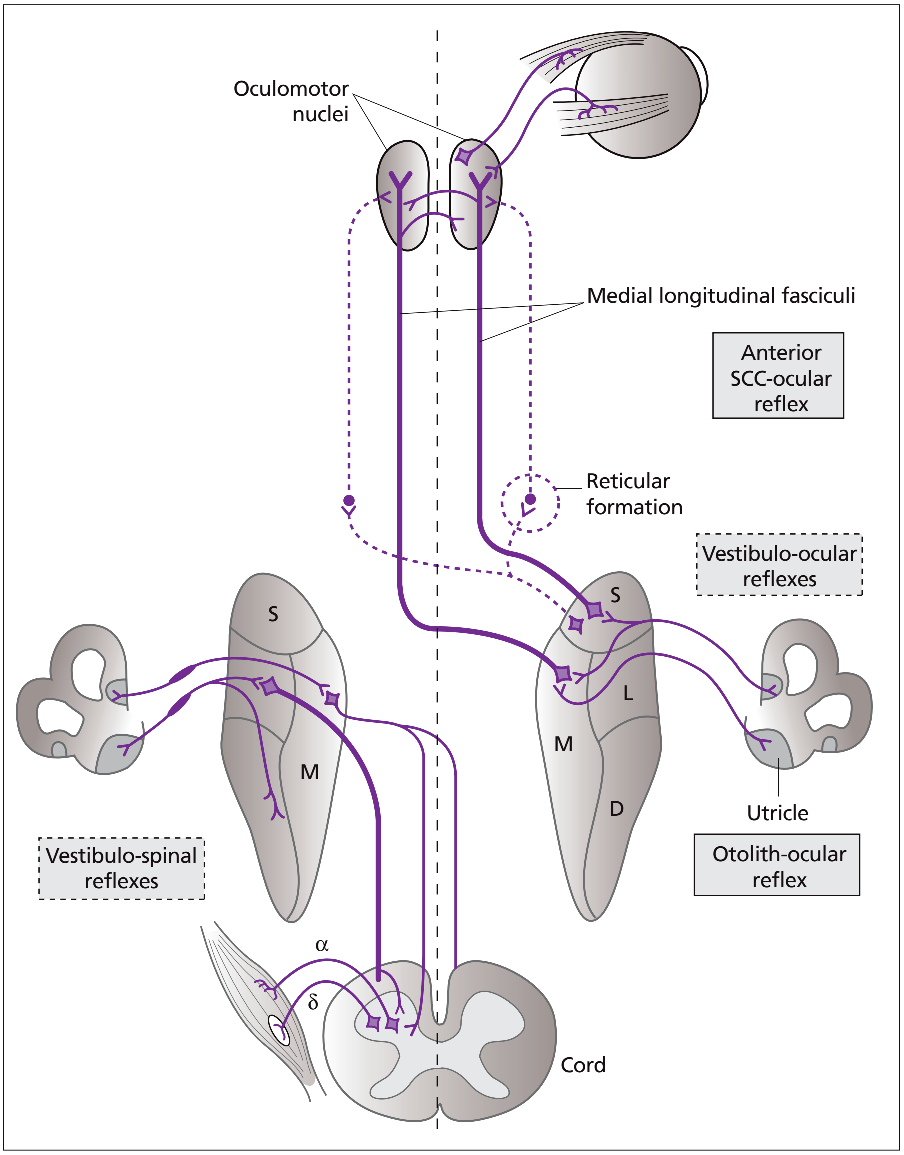
Oculomotor nuclei
Medial longitudinal fasciculi
Anterior SCC-ocular reflex
Reticular formation
Vestibulo-ocular reflexes
S
S
L
M
M
D
Utricle
Otolith-ocular reflex
Vestibulo-spinal reflexes
α
δ
Cord

Figure 14.1 Vestibulo-ocular and vestibulo-spinal reflexes. S, L, M, D: superior, lateral, medial and descending vestibular nuclei; SCC, semicircular canal. (From Brodal 1981, with permission.)

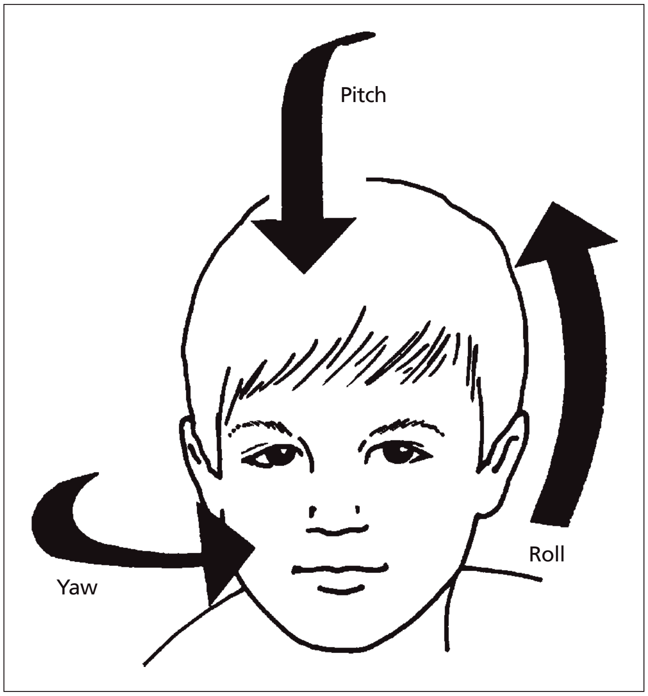
Pitch
Roll
Yaw

Figure 14.2 Three-dimensional planes of head movement. (From Savundra & Luxon 1997, with permission.)

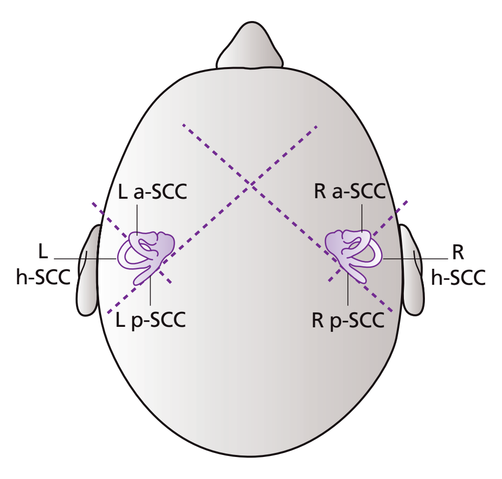

Figure 14.3 Topographic orientation of anterior, horizontal and posterior semicircular canals. a-SCC, anterior semicircular canal; h-SCC, horizontal semicircular canal; p-SCC: posterior semicircular canal. (From Rudge 1993, with permission.)

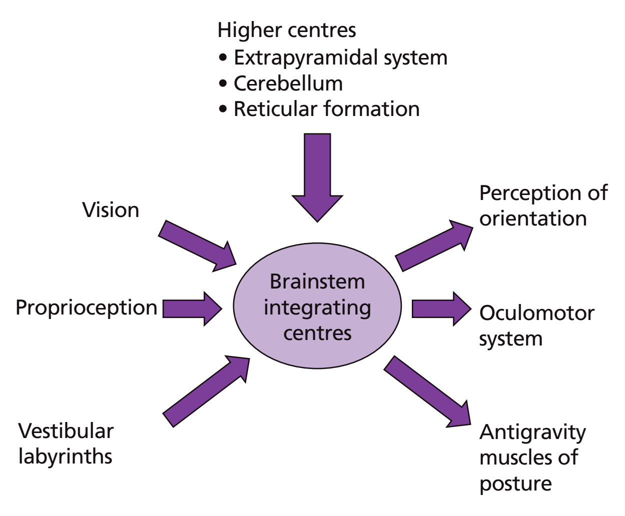

Figure 14.4 The three sensory inputs maintaining equilibrium, central modulating influences and efferent pathways. (From Davies 2004, with permission.)

This alignment, between spatial planes of the three semicircular canals and the planes of the three sets of extraocular muscles is such that when the two paired labyrinths are excited, the two eyes move conjugately, i.e. they are yoked – producing an appropriately directed compensatory eye movement. This is the vestibulo-oculo reflex. The paired horizontal semicircular canals function as a gauge of rotational acceleration in the yaw plane and are connected via the brainstem nuclei to the set of extraocular muscles whose primary direction of pull is also in the horizontal plane – lateral and medial recti. The action of these muscles is to produce compensatory eye movement in the horizontal plane in an equal and opposite direction to that of head movement, maintaining stable gaze.

The neuronal circuitry is similar for the vertical planes of pitch and roll: the anterior and posterior semicircular canals, sited diagonally to the sagittal plane are connected to the paired extraocular muscles whose primary action is aligned to the spatial planes of each canal (Fig. 14.3). Thus, the superior and inferior recti move the eye up or down when that eye is abducted; the inferior and superior oblique muscles move the eye up and down when it is adducted. The system is driven by the relationship between endolymph and cristae (Chapter 2). The relevant principles were described by Ewald in 1892:

1 Head and eye movements always take place in the plane of the canal that is stimulated and in the direction of endolymph flow.

2 In the horizontal canal, endolymph flow towards the ampulla (ampullo-petal) causes a greater response than endolymph flow away from the ampulla (ampullo-fugal).

3 In the vertical canals, endolymph flow away from the ampulla (ampullo-fugal) causes a greater response than endolymph flow towards the ampulla (ampullo-petal).

Encoding of head movements in space

Sensory epithelium of each vestibular end organ includes the maculae of the utricle and saccule and the cristae, found in the ampullae of the three semicircular canals. Both maculae and cristae contain sensory hair cells with projecting kinocilia. Linear acceleration and gravitational forces are transduced by the otolith organs of the utricle and saccule; angular acceleration is transduced by the cristae. As a result of the orientation of the semicircular canals and arrangement of hair cells, head movements in any plane are encoded by the pattern of deflection of kinocilia. Stabilizing sensory information thus derived is relayed to the vestibular nuclei, integrated and stored in a data centre probably within the reticular formation. New sensory data are constantly compared with this data bank; under normal circumstances, there is a match between visual, proprioceptive and vestibular inputs, thus maintaining equilibrium (Fig. 14.4). This matching up of sensory inputs is essential for spatial orientation and perception of motion. Vertigo results from a mismatch between sensory information from these inputs, leading to impaired perception of a stationary environment. Vestibular sensations can also occur as a response to a moving environment, e.g. motion sickness, or with pathology of any of the three sensory stabilizing systems. Examples of the latter include disturbed labyrinthine input during an attack of Ménière's disease, altered visual input with the initial use of varifocal contact lenses or with impaired proprioception following a knee joint replacement. The unpleasant autonomic sensations of nausea, vomiting and anxiety that often accompany vertigo are mediated by vestibulo-autonomic pathways.

Eye movements

To achieve clarity of vision, a prerequisite to respond accurately and appropriately to the environment, an image must be held steady on the retina, ideally on the fovea where the photoreceptor density is greatest (Chapter 2). For best resolution, retinal image motion should be <5°/second. From a neuro-otological perspective, eye movements are of two types:

1 Eye movements that stabilize the angle of gaze; and
2 Eye movements that change the angle of gaze.

Eye movements that stabilize the angle of gaze

Reflexes that allow stabilization of the retinal image during head movements are:

1 Vestibulo-ocular reflexes (VOR)
2 Visually mediated reflexes:
  (a) Optokinetic (OKN);
  (b) Smooth pursuit tracking.

Without these reflexes visual images would slip on the retina with each head movement and cause blurred vision. Stability depends both on the brain's ability to judge this speed of retinal image drift and the fovea being directed at the object of interest, by conjugate mechanisms.

Eye movements that change the angle of gaze

With a new object of interest, eye movements that redirect the direction of gaze are:

1 Nystagmic quick phases;
2 Saccades; and
3 Vergence movements.

In animals lacking a fovea, a rapid eye movement (nystagmic quick phase) is linked to voluntary head movement to override the dominant optokinetic and vestibular drives to eye movement. In animals with a fovea, various mechanisms exist to point this central retinal portion to the new object, i.e. the direction of gaze is changed, independently of head movement by a voluntary saccadic rapid eye movement. With evolution of binocular vision, vergent (converging) eye movements have also developed to maintain the image on each fovea simultaneously (Table 14.1).

Patients with bilaterally defective labyrinths can generate all the smooth eye movements required to stabilize gaze using cervico-ocular reflexes (COR) and OKN reflexes when head movements are slow. However, if they turn their heads rapidly, i.e. >1 Hz or 100°/s peak velocity, compensatory eye movements will be too slow – saccades have to be generated to stabilize gaze: the patients experience oscillopsia – bobbing vision – and, as with nystagmus, an illusion of movement of the surroundings. Gaze error accumulates during head movement and is finally corrected by oppositely directed compensatory saccades.

Mechanisms of dizziness

One approach to dizziness is to consider that the sensation can be caused by:

1 Sensory mismatch;
2 Multisensory disturbances;
3 Presyncopal light-headedness; and
4 Physiological and psychological factors affecting central integration of sensory inputs.

Sensory mismatch

When any vestibular sensory input is disturbed there is initially a marked disequilibrium, e.g. the violent vertigo of vestibular neuritis. Compensation then develops via CNS plasticity mechanisms and sensory substitution within the central integrating system. Symptoms improve or subside.

Multisensory dizziness

If two or more sensory systems are perturbed together, compensation is prolonged and may remain incomplete. Multisensory dizziness describes this situation in which multiple stabilizing sensory inputs are impaired, e.g. an elderly patient with impaired vision, impaired proprioception because of restricted neck movement with an additional peripheral vestibular deficit following a minor head injury (Fig. 14.4).

Presyncopal light-headedness

This arises from impaired cerebral blood flow to the vestibular nuclei and experienced by all, e.g. standing up rapidly from a supine or seated position. The sensation also occurs during hyperventilation, with orthostatic hypotension or anaemia and during a cardiac dysrhythmia.

Table 14.1 Classes of eye movement in relation to function. (After Leigh & Zee 2006, with permission.)

Class	Main function
Vestibular (VOR)	Holds images steady on retina during brief head rotations or translations. Only VOR is fast enough to keep up with natural head movements
Visual fixation	Holds image of stationary object on fovea by minimizing ocular drift
Optokinetic (OKN)	Holds image steady on retina during sustained head rotation
Smooth pursuit	Holds image of a small moving target on fovea or holds image of a small near target on retina during linear self-motion: with optokinetic responses, aids gaze stabilization during sustained head rotation
Nystagmic quick phases	Reset visual axes during prolonged rotation and direct eyes toward the oncoming visual scene
Saccades	Bring images of interest on to fovea
Vergence	Moves eyes in opposite directions (i.e. to converge) so that images of a single object are placed simultaneously on fovea of each eye

VOR, vestibulo-ocular reflexes.

Table 14.2 Symptoms helpful in localization of vestibular lesions.

Site of lesion	Symptoms
Inner ear	Tinnitus, hearing loss, aural fullness, otalgia
VIIIth nerve/IAM	Poor speech discrimination, facial weakness
Cerebellopontine angle	Impaired facial sensation, clumsiness, dysarthria, incoordination
Brainstem	Hemisensory loss, hemiparesis, cranial nerve palsies, dysarthria, dysphagia, memory disturbances, loss of consciousness
Cerebellum	Incoordination, clumsiness, dysarthria
Cortex	Olfactory/gustatory hallucinations, vertiginous seizures

IAM, internal auditory meatus

Physiological and psychological dizziness

This includes effects of drugs that interfere with central integration of sensory inputs, e.g. anticonvulsants and minor tranquillizers. Psychological phenomena, e.g. panic attacks, anxiety and/or mismatch of visual perceptions, account for dizziness at heights or in precarious situations.

The dizzy patient: diagnostic strategy

From the history, ascertain whether or not vertigo is present and the nature of symptoms encapsulated by the word dizziness. Attention to verbatim details is important.

Vestibular symptoms

Symptoms of vestibular dysfunction are often similar whether the site of pathology is within the vestibular end organ, in the labyrinth, of VIIIth nerve origin or within the central pathways. Siting a lesion can be difficult. Various features in the history and associated symptoms help distinguish between peripheral (otological), central (neurological) and general medical causes.

Associated symptoms

The traditional approach to diagnosis is to distinguish peripheral from central disorders using the simple strategy of noting whether dizziness is isolated or whether it is associated with symptoms arising from the ear. In the latter situation, a crude site-of-lesion diagnosis points to the disorder being otological, i.e. peripheral. If vertigo is associated with neurological symptoms, the problem has a central source. It is widely accepted that isolated prolonged vertigo without neurological features rarely has a central origin, because of the proximity between vestibular nuclei and other brainstem structures (Table 14.2). Although a useful generalization, it is important to keep an open brief: acute vertigo alone can be central in origin, e.g. a posterior circulation infarct (Chapter 4).

Table 14.3 Triggers to vertigo.

Trigger	Diagnosis
Spontaneous	Vestibular neuritis; benign recurrent vertigo, migrainous vertigo
Head positioning	Benign paroxysmal positional vertigo (of posterior, horizontal and anterior semicircular canal type); central positional vertigo
Head turning	Vestibular paroxysmia; carotid sinus hypersensitivity
Head movement	Incompletely compensated peripheral vestibular deficit
Visual motion	Visual vertigo; incompletely compensated peripheral vestibular deficit; migraine-related dizziness
Coughing/straining/low frequency sound	Anterior semicircular canal dehiscence; perilymph fistula

Table 14.4 Duration of vertigo.

Duration	Diagnosis
Seconds to minutes	Benign paroxysmal positioning vertigo; vestibular paroxysmia; vertiginous epilepsy
Minutes to hours	Transient ischaemic attacks of brainstem or cerebellum, migrainous vertigo
Hours	Ménière's disease; vestibular migraine
Sustained – days to weeks	Vestibular neuritis; MS lesions

MS, multiple sclerosis.

Triggers to vertigo

Triggers to vestibular symptoms can be helpful. If a patient reports any of the five typical triggers for benign paroxysmal positional vertigo (BPVV) – lying down or rolling over in bed, sitting up, extending or flexing the neck, a head-positioning manoeuvre such as the Dix–Hallpike test will help confirm or exclude BPPV. Other triggers suggesting specific diagnoses for vertigo are shown in Table 14.3.

Duration of vertigo

The duration of vertigo can also be helpful (Table 14.4). For example, the typical severe vertigo of untreated Ménière's disease lasts 2–24 hours.

Classification of vestibular disorders

Tables 14.5 and 14.6 divide disorders by peripheral, central and general medical origins. Individual conditions specific to neuro-otology are discussed later.

Table 14.5 Causes of peripheral and central vestibular problems.

Peripheral

Middle ear pathology

Perilymph fistula (trauma, cholesteatoma, surgery)
Serous otitis media (glue ear)
Chronic middle ear disease, e.g. suppurative otitis media

Peripheral vestibular pathology

Vestibular neuritis
Benign paroxysmal positional vertigo
Bilateral vestibular failure
Anterior semicircular canal dehiscence
Ménière's disease
Vestibular paroxysmia

VIIIth nerve lesion

Vestibular schwannoma
Neurofibromatosis type 2
Other cerebellopontine angle tumour
Basal meningitis, e.g. tuberculous meningitis
Neurosarcoidosis
Lyme disease

Central

Mendelian heritability

Friedreich's ataxia
Arnold–Chiari malformations
Spino-cerebellar ataxias
Episodic ataxias (types 1 and 2)

Others

Migrainous vertigo
Multiple sclerosis
Posterior fossa mass lesions
Syringomyelia and syringobulbia
Posterior circulation ischaemia/infarction
Inflammatory disorders
Malignant meningitis
Multisystem atrophy
Vestibular epilepsy
Raised intracranial pressure
Drugs

Table 14.6 General medical causes of vestibular symptoms.

Orthostatic hypotension i.e. reduction of >20 mmHg systolic blood pressure measured 0–3 min after assuming an upright posture after lying for 10 min	Causes: • Prolonged bed rest • Hypotensives, major tranquillizers, vasodilators, antidepressants, beta-blockers, levodopa • Autonomic neuropathy, e.g. diabetes, Shy–Drager syndrome • Hyponatraemia, Addison's disease, chronic renal failure
Vasovagal episodes characterized by sense of hearing and vision receding, buzzing in the ears and sense of impending doom, light-headedness	Triggers: • Standing at attention for too long • Noxious stimuli • Vertigo • Fear, emotional stress • Hot stuffy environments
Low cardiac output	• Cardiac dysrhythmia • Stokes–Adams attack • Carotid sinus hypersensitivity • Aortic stenosis • Hypertrophic cardiomyopathy
Hyperventilation	Clinical features include: • Muscle cramps, carpopedal spasm • Breathlessness, air hunger • Palpitation, chest tightness
Other	• Hypoglycaemia • Anaemia • Many acute illnesses, e.g. infections • Chronic fatigue syndrome

Neuro-otological assessment

Assessment may be needed urgently during acute vertigo, or subsequently, when complementary tests may be required. Examination is directed towards detecting abnormalities of gait, eye movement and any associated otological, neurological or general medical problem. Assess any factors that compromise the value of physical signs, such as anxiety. The majority of vertiginous patients are highly unlikely to have any mass lesion, but overreliance on normal imaging can lead to missing common conditions, such as BPPV or failure to compensate following vestibular neuritis. The targets are to identify the site of the problem, to gather information leading to an aetiological diagnosis and to formulate a management plan. Most tests are simple. They can be carried out at the bedside or in a clinic (Table 14.7); not all tests are necessary in every case.

Eye movements

The basic concepts described above are applied to anyone with a vestibular disorder, and require optimal conditions: good lighting and comfortable seating with the patient's head erect.

Assess:

- Visual acuity (a 6-m Snellen chart, or a hand-held chart);
- Visual fields in each eye (by confrontation); and
- Eye movement – initially, with eyes in the primary position of gaze, in the same horizontal plane as the examiner's eyes, with the target at a distance just greater than the patient's focal point.

Table 14.7 Routine neuro-otological examination.

Eye movements
Static
A. Cover test for strabismus, latent nystagmus

Dynamic
B. Range of eye movements and gaze testing
C. Saccades
D. Smooth pursuit
E. Optokinetic nystagmus
F. Assessment of nystagmus
G. Dix–Hallpike test and supine roll test for positional nystagmus
H. Halmagyi headthrust test

Gait and stance
I. Romberg's test
J. Unterberger's test
K. Gait testing
L. Tandem gait testing

Ear and hearing
M. Otoscopy
N. Tuning fork tests

Cover test

Misalignment of the visual axes needs to be identified, i.e. manifest or latent strabismus. Either can lead to eye movement abnormalities, because fixation switches from one eye to the other. If one eye has become amblyopic, the better eye should be assessed, both by clinical tests and electronystagmography (ENG). Commonly, a patient with acquired strabismus will turn or tilt their head to minimize diplopia. Turning is seen typically with paresis of a horizontal extraocular muscle, e.g. following VIth nerve palsy, when the head is turned towards the weak lateral rectus. Following a IVth nerve palsy, the head tends to tilt, if slightly, towards the side of the weak superior oblique.

To perform the cover test, the patient is asked to fixate a distant target, with refractive correction in place. Each eye is covered in turn; this prevents foveal fixation by the covered eye. The cover test relies on the fact that foveation occurs in the eye forced to fixate; movement redress occurs if the retinal image was not directed to the fovea before the eye took up fixation. The patient is asked to fixate with the uncovered eye on a target; the covered eye is then observed as the cover is removed.

Horizontal misalignment

Manifest strabismus

A squint is seen when the visual axes of the two eyes deviate with the eyes uncovered:

- An exotropion (divergent squint) means that the affected eye is turned outwards in primary gaze;
- An esotropion (convergent squint) means that the eye is turned inward in primary gaze.

Latent strabismus

This describes the situation when misalignment is corrected spontaneously by fusional mechanisms when both eyes are uncovered, i.e. the problem becomes apparent only on cover testing:

- Exophoria is identified when the eye moves inward as the cover is removed;
- Esophoria is identified when the eye moves outwards with refixation.

Latent nystagmus

Nystagmus is seen in the uncovered eye during cover testing. Typically, the nystagmus beats away from the covered eye and is conjugate. Latent nystagmus can be unilateral or bilateral. Some cases are associated with congenital nystagmus (see below).

Vertical misalignment

Skew deviation

This is a vertical misalignment of the visual axes. Skew deviation is a vertical tropia, and may be either a hypotropia (uncovered eye moves up as the other is covered) or a hypertropia (the uncovered eye moves down as the other is covered). By convention, the higher of the eyes is referred to as hypertrophic/hyperphoric, regardless of which is at fault. The hypertropia may be the same in nearly all positions of gaze (concomitant) or vary with right or left gaze (non-concomitant) and is usually associated with the ocular tilt reaction (OTR). When it is non-concomitant, skew deviation can be distinguished from a superior oblique palsy by the direction of any torsion of the elevated eye (intorsion with a skew, extorsion with a IVth nerve palsy). Skew deviation can be either sustained or paroxysmal. Skew deviation is caused typically by brainstem or cerebellar lesions.

Ocular tilt reaction

The OTR is an abnormal response to head tilt. The examiner recognizes an OTR from head tilt, skew deviation and cyclotorsion. Usually there is hypotropion. The head tilt is towards the lower eye, and the upper poles of the eyes rotate towards the lower ear. Patients with an OTR show a deviation of the subjective visual vertical, i.e. if they draw a line they believe to be vertical, it will not be so.

The OTR is part of a primitive righting response to lateral head tilt. In lateral eyed animals, tilting the head around the longitudinal axis causes a non-conjugate vertical (skew) deviation (one eye goes up, the other down) to hold the visual axis of each eye close to the horizon. In humans, a static head tilt (ear to shoulder) causes sustained conjugate counter-rolling of the eyes equal to 10% of the head roll. An OTR is attributed to an imbalance in otolith–ocular inputs and otolith–collic reflexes.

Pathological tilts of the subjective visual vertical and ocular torsion are sensitive signs of brainstem infarction: assessment of OTR is an important part of examination in any acute vertigo. Two types of OTR are described, corresponding to current concepts:

1 Ascending ponto-medullary VOR-OTR with ipsilateral lesions of roll VOR pathways close to the vestibular nuclei and characterized by dysconjugate ocular torsion, e.g. Wallenberg's syndrome (Chapter 4).

2 Descending mesencephalic integrator OTR with contralateral lesions of the midbrain integration centres (interstitial nucleus of Cajal, medial longitudinal fasciculus) and characterized by conjugate ocular torsion.

Range of eye movements and gaze testing

The eyes are examined in both horizontal and vertical planes to a limit of 30° from the horizontal and 20° from vertical meridian. Movements are conjugate (yoked) when both eyes move together at the same velocity, and disconjugate when one eye moves more slowly than the other, or movement of one eye is incomplete. If movements are conjugate but their range is incomplete, the likely cause is a gaze paresis.

Gaze paresis

A gaze paresis occurs if there is a restriction in the range of conjugate movement, in one or more directions. It may be nuclear or supra-nuclear, with reference to the oculomotor nuclei:

- Contralateral horizontal gaze paresis occurs in lesions of the frontal eye fields and the cortex;
- Ipsilateral gaze paresis follows lesions of the tegmentum, ponto-medullary or ponto-mesencephalic junctions;
- Supra-nuclear gaze palsy can be seen in mesencephalic lesions, in which there is loss of volitional gaze, with vertical movements being lost before horizontal. This is identified by finding a full range of eye movements in response to involuntary reflex testing, i.e. vertical VOR testing.

Ocular muscle paresis

Where there is a dissociation of eye movements, i.e. they are disconjugate, an ocular muscle paresis is likely (Chapters 3 and 13). Alternative explanations include a non-comitant strabismus or a central lesion such as an internuclear ophthalmoplegia. The eyes should be examined for IIIrd, IVth and VIth nerve palsies by examining the range of movement in each eye individually (ductions). The oblique muscles are tested when the eye is adducted. The superior oblique, through its pulley system depresses the eye; conversely the inferior oblique elevates it. The vertical recti are tested with the eye abducted. The inferior rectus lowers the eye; superior rectus elevates it.

An ocular muscle paresis may either be congenital, e.g. Möbius' syndrome (Chapter 13), or acquired, e.g. due to a retro-orbital space-occupying lesion due to involvement of the extraocular muscles, e.g. thyroid eye disease or mitochondrial cytopathy; due to manifest strabismus; or due to lesions of the IIIrd, IVth and VIth cranial nerves, or their nuclei, each causing paresis in the direction of the pull of the muscles innervated:

- A IIIrd nerve lesion causes the eye to be drawn down and out, and is associated with ptosis and a dilated pupil when the damage involves parasympathetic fibres;
- A IVth nerve lesion causes torsional diplopia on looking down, and a head tilt (i.e. ear to shoulder) away from the side of the weakness;
- A VIth nerve lesion causes loss of abduction and horizontal diplopia. The head may compensate by turning towards the side of the lesion.

Saccades

Saccades are fast eye movements (velocity 350–600°/s), the velocity increasing with increasing amplitude of eye movement. Saccades can be voluntary or involuntary, the former moving the eyes between visual targets in the shortest possible time. Involuntary saccades maintain the target on the fovea when there has been slip of the retinal image, e.g. following the vestibular, slow phase of nystagmus. The saccade may be visually triggered, as in optokinetic nystagmus, or can be of vestibular or cervical origin. Normal subjects are accurate up to a target jump of 20°, above which a small corrective saccade is required to bring the fovea on target. Overshooting is rare. The normal saccadic latency before a new saccade can be generated is 200 ms.

The ability to generate saccades depends on the integrity of projections between the frontal eye fields, the caudate nucleus, the substantia nigra reticulata and the deep and intermediate layers of the superior colliculus (Chapters 2 and 13). Projections are to the parapontine reticular formation (PPRF) and thence to the ipsilateral VIth nucleus and via the median longitudinal fasciculus (MLF) to the contralateral IIIrd nucleus (medial rectus) for saccades in the horizontal plane. Pretectal neurones also project to the oculomotor nuclei, both sets of neurones connecting to the vestibular nuclei.

Clinical assessment of saccadic eye movements

Saccadic eye movements are assessed by asking the patient to look back and forth between two targets, e.g. tendon hammer shaft. Each direction is examined, assessing eye movements to 30° right and left of the midline in the horizontal plane, and 20° above and below midline in the vertical plane.

Abnormalities of saccadic eye movements

Four variables are examined: saccadic velocity; saccadic accuracy and saccadic initiation time (latency) – and whether the eyes move together. Abnormalities may be brought about by CNS pathology, strabismus (see above) or ocular muscle involvement. Peripheral vestibular pathology does not cause abnormal saccadic eye movements.

Internuclear ophthalmoplegia (INO) is caused by a lesion of the ipsilateral medial longitudinal fasciculus (MLF) and is recognized primarily by a lag in the adducting eye and nystagmus in the abducting eye. This is best observed when the patient is asked to refixate rapidly between two targets widely spaced. Subtle early lesions can be revealed by ENG recordings (Fig. 14.5) of separate eye saccades, showing slowing of the adducting saccade ipsilateral to the lesion, with a hyper-metric, and normal velocity saccade, followed by a gaze-evoked nystagmus in the abducting eye.

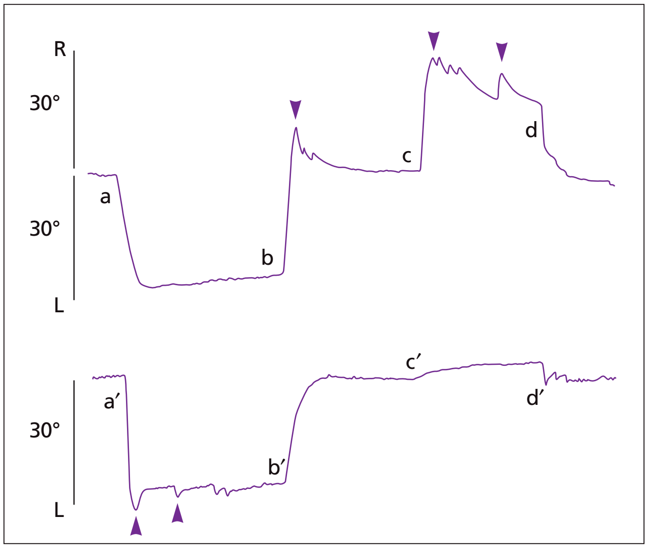

Figure 14.5 ENG tracing of internuclear ophthalmoplegia (INO). Upper trace shows movements of the right eye; lower trace shows those of the left. At point a/a′ the eyes are looking straight ahead. At b/b′ the eyes are at 30° to the left. At c/c′ the eyes are again looking straight ahead. At d/d′ the eyes are at 30° to the right. The trace identifies a left INO with failure of the left eye to adduct (d′) and nystagmus in the abducting right eye (d). (From Davies 2004, with permission.)

Lesions of the PPRF cause slowing and eventual loss of rapid ipsilateral movements in the horizontal plane when the eyes move to the contralateral visual field. In response to vestibular or visual stimulation, the eyes display a tonic contralateral deviation with loss of the fast phase of nystagmus.

The pattern known as ‘one-and-a-half’ syndrome consists of failure of horizontal conjugate gaze in one direction and INO in the other. This is seen with extensive brainstem pathology affecting both ipsilateral PPRF and MLF, and not uncommonly found in advanced MS.

Cerebellar pathology can affect accuracy of saccades with undershooting (hypometria) due to lesions in the dorsal vermis, and/or overshooting (hypermetria) due to lesions in the fastigial nucleus. Normal individuals may undershoot the target by a few degrees when the refixation angle is large, and may overshoot with saccades directed back towards the midline, particularly if these are in a downward direction.

In lesions of the frontal eye field, there is an increased latency of saccades to remembered targets. In basal ganglia lesions there are difficulties initiating voluntary saccades for tasks that require learned or predictive behaviour (Chapter 2).

Supranuclear degeneration occurs in multisystem atrophy (including progressive supranuclear palsy). There is an increased latency to saccadic reaction time. Vertical eye movements are usually affected before horizontal, initially with down-gaze more involved than up-gaze, with saccades affected more than pursuit.

The pathways subserving vertical and horizontal saccades are largely independent, such that vertical saccades are unimpaired by lesions of the PPRF, while lesions of the mesencephalic reticular formation affect vertical saccades exclusively.

A further localizing strategy is to determine whether there is a loss of voluntary saccades (e.g. to see if saccades can be made with an auditory target), or whether or not there is loss of reflexive saccades (i.e. eliciting OKN with a hand-held drum). When there is loss of voluntary saccades with preservation of reflexive saccades and quick phases, this is characteristic of oculomotor apraxia.

Smooth pursuit

Smooth pursuit is responsible for maintaining gaze on a moving target so that the target remains stabilized on the fovea. The gain of the pursuit system approaches unity at peak velocities of 30°/s or sinusoidal rotation at 0.1 Hz. Above a peak velocity of 60°/s (or sinusoidal rotation at 1 Hz) the gain falls off rapidly: saccades, described as catch-up in character, are seen, i.e. saccadic intrusions, and the pursuit movement becomes broken. The smooth pursuit and the vestibulo-ocular reflex system are complementary in stabilizing the retinal image, with the pursuit system efficient at low target velocities and the vestibulo-ocular system efficient at high input velocities.

Clinical assessment of smooth pursuit

The smooth pursuit system can be examined clinically by moving a target, e.g. a tendon hammer shaft, slowly back and forth, initially in the horizontal and then in the vertical plane, to a maximum of 30° displacement from the midline, at 0.2–0.4 Hz. In chronic peripheral vestibular disorders, smooth pursuit is normal.

Abnormalities of smooth pursuit

Lesions of the fovea, of the calcarine cortex, of the parieto-occipital cortex, the parieto-temporal region, the dorso-lateral pontine nucleus and the cerebellar-flocculus cause ipsilateral or bilateral abnormalities. Pursuit eye movements are symmetrically affected by age, psychotropic medication, alcohol, anticonvulsants and vestibular and CNS sedatives – this range of causes limits their diagnostic value, but otherwise, testing pursuit has high sensitivity to identify central vestibular dysfunction.

Optokinetic nystagmus

The function of optokinetic nystagmus (OKN) is thought to be stabilization of the eyes relative to space during slow head movements in the low frequency range, ill-served by the VOR. OKN is the jerk nystagmus seen commonly when people gaze out of a train window. The optokinetic system includes the peripheral retina, accessory optic tract, vestibular nuclei and the reticular formation. There are two types of OKN:

1 *Cortical optokinetic nystagmus*: known as active, or ‘look OKN’ – induced mainly through foveal input. This can be induced both by using a small drum and by a full-field OK stimulus.

2 *Subcortical optokinetic nystagmus*: known as passive, or ‘stare OKN’. It is believed that the peripheral retina is involved without participation of the cortex.

In the active situation (look OKN), the slow component velocity is similar to the speed of the drum, i.e. the gain approaches unity. Also, with reversal of the drum direction, the eyes deviate in the direction of the slow component, i.e. in the direction of movement of the drum. In stare OKN, subserved by the subcortical pathway, the slow component velocity is consistently less than drum velocity. With drum reversal, the direction of eye deviation is in the direction of the fast phase of the nystagmus.

Clinical assessment of OKN

Simple qualitative assessment uses a small hand-held or mechanically driven optokinetic drum. This is a 30-cm diameter striped cylinder, rotated to elicit nystagmus in either horizontal or vertical planes, at speeds around 40°/s upwards. A rolled-up tapemeasure run out from the examiner’s hand is a useful improvization. For quantitative purposes, more precise stimulus parameters are obtained by seating the patient inside a large striped rotating drum and stimulating the entire visual field.

Abnormalities of OKN

The hand-held OKN drum is often helpful to confirm lateralization of an abnormality and is of some value in sorting out peripheral and central lesions, and congenital nystagmus.

Peripheral lesions. Imbalance of vestibular tone resulting from lesions of the labyrinth and VIIIth nerve can give rise to a directional preponderance with the hand-held drum. This is seen best by direct observation of eye movements in response to repeated abrupt reversal of the drum direction. These abnormalities are rarely seen with full-field OKN.

Central lesions. Abnormalities of OKN tend to mirror abnormalities of smooth pursuit, and abnormalities of fast components mirror abnormalities of voluntary saccades. Lateralized lesions of the parieto-occipital region, brainstem and cerebellum result in impaired OKN when the stimulus is moved toward the damaged side.

Congenital nystagmus. Reversal of OKN is a significant feature in many cases of congenital nystagmus. The nystagmus beats paradoxically, in the direction opposite to that anticipated from that of the drum (Fig. 14.6).

Assessment of nystagmus

Jerk nystagmus is a sequence of slow and fast phase eye movements, alternating back and forth. For clinical purposes the direction of nystagmus is defined by the fast phase. Nystagmus can be physiological or pathological. Pathological nystagmus is either congenital or acquired. Generally, large amplitude nystagmus should be considered to be central in origin; it is only likely to be peripheral if seen clinically in the first few days of vestibular neuritis or an acute episode of Ménière’s disease. Fine amplitude nystagmus can either be central or peripheral in origin.

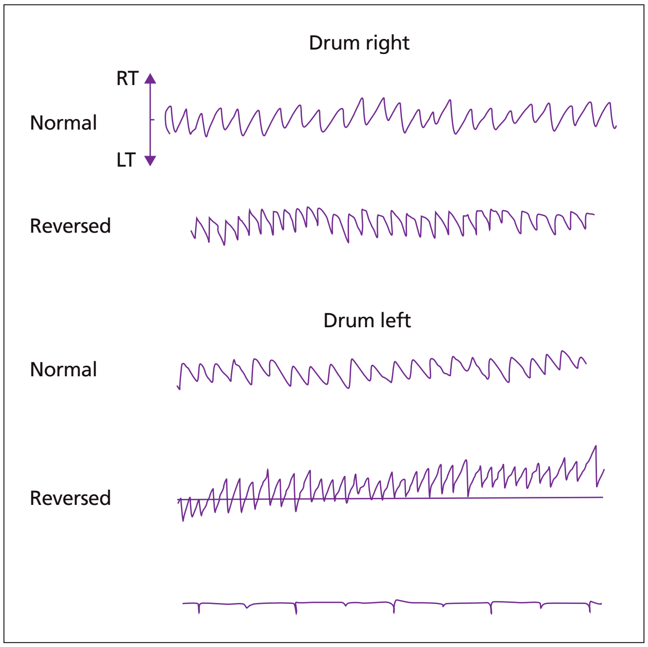

Figure 14.6 Congenital nystagmus, showing reversal of optokinetic nystagmus (OKN), with the slow phase of the patient’s eyes in the opposite direction to that of the drum. (From Hood 1984, with permission.)

Physiological vestibular nystagmus

With small amplitudes of head displacement, there is a slow compensatory eye movement in the direction opposite to rotation, serving to stabilize the gaze. With a greater stimulus the slow vestibular-induced eye movement deviation is interrupted by a fast eye movement in the opposite direction, generating physiological nystagmus. This type of nystagmus can be induced both by rotary chair testing and caloric irrigations but also by extremes of eye deviation, i.e. more than 30° laterally from the primary position (physiological endpoint nystagmus). There is a relationship between the magnitude of nystagmus and the state of arousal. A subject who is allowed to daydream has a lower slow component velocity than one asked to perform continuous mental arithmetic. Subjects experiencing repeated angular accelerations, e.g. ice skaters and dancers, may display permanent habituation of the response with a reduction or loss of nystagmus in response to vestibular stimulation.

Pathological vestibular nystagmus

Spontaneous nystagmus results from an imbalance of tonic signals arriving at the oculomotor nuclear neurones. Because the vestibular system is the main source of oculomotor tonus, it is the driving force of most types of spontaneous nystagmus. There is a constant drift of the eyes towards the side of the lesion, interrupted by a fast component in the opposite direction. The lesion may be within the labyrinth, the vestibular nerve, in the vestibular nuclei or their connections.

The pattern of nystagmus can be valuable in siting the lesion. Full assessment includes observation of the nystagmic response produced by change of eye position and the removal of optic fixation, i.e. using Frenzel's glasses or video-oculography, with grading of nystagmus in different positions of gaze. This grading is known as Alexander's law. Nystagmus is present:

1 When the eyes are deviated towards the fast phase of nystagmus;
2 When nystagmus is also seen in the primary position; and
3 If it is also seen with the eyes deviated towards the slow phase.

If a vestibular lesion is small or compensation at a central level has occurred, nystagmus may be detectable only when optic fixation is removed. This is an important criterion for identifying nystagmus brought about by peripheral pathology, i.e. the nystagmus displays an increase of amplitude with the removal of optic fixation.

Gaze evoked nystagmus

Patients with gaze evoked nystagmus are unable to maintain stable conjugate eye deviation away from the primary position. The eyes drift backwards towards the centre with an exponentially decreasing waveform. Corrective saccades constantly reset the eyes to the desired position; thus, gaze evoked nystagmus is always in the direction of gaze. In the absence of optic fixation, the frequency and slow component velocity decrease. Dysfunction may be secondary to a lesion anywhere from the multiple brain centres controlling conjugate gaze to the neuromuscular junction. Symmetrical gaze evoked nystagmus is commonly observed with anticonvulsants, particularly with phenytoin or phenobarbital when the blood levels are higher than the normal therapeutic range. This is also seen in alcohol intoxication and following various psychotropic drugs. Horizontal gaze evoked nystagmus that is asymmetrical is likely to indicate a structural brain lesion. However, asymmetrical jerking movements are sometimes seen in myasthenia gravis. Gaze evoked nystagmus is not brought about by a peripheral vestibular lesion.

Positional nystagmus, Dix–Hallpike and Roll manoeuvres

Peripheral positional nystagmus

Peripheral positional nystagmus occurs in BPPV. This condition is usually diagnosed from the history and confirmed using the Dix–Hallpike and supine roll manoeuvres. With the pathological ear undermost, the Dix–Hallpike manoeuvre and Roll manoeuvre produce characteristic signs (Table 14.8).

Table 14.8 Characteristic features of different types of positional nystagmus.

	p-BPPV	h-BPPV geotropic	h-BPPV apogeotropic	a-BPPV	Central
History	Vertigo on turning over in bed, getting in or out of bed, looking up or down	Vertigo on rolling from side to side in bed	Same as for geotropic h-BPPV	Same as for p-BPPV	Often little in the way of positional vertigo
Diagnostic positional test	Hallpike or side-lying (on affected side)	Supine roll test	Supine roll test	Hallpike, or side-lying (on opposite side)	Hallpike
Latency	2–20 s	<5 s	Nil	2–20 s	Nil
Nystagmus	Torsional (geotropic)/vertical (upward) with head tilt in the plane of the posterior canal	Horizontal (geotropic) more marked towards affected ear	Horizontal (apogeotropic) more marked towards affected ear	Vertical (downbeat)/small torsional component towards affected ear	Pure vertical or torsional not direction changing
Duration	<40 s			<40 s	>60 s
Reversibility	On sitting	On rolling to other side	On rolling to other side	On sitting	No
Fatiguability	Yes	No	No	Variable	No

a-BPPV, anterior canal benign paroxysmal positional vertigo; h-BPPV, horizontal canal benign paroxysmal positional vertigo; p-BPPV, posterior canal benign paroxysmal positional vertigo.

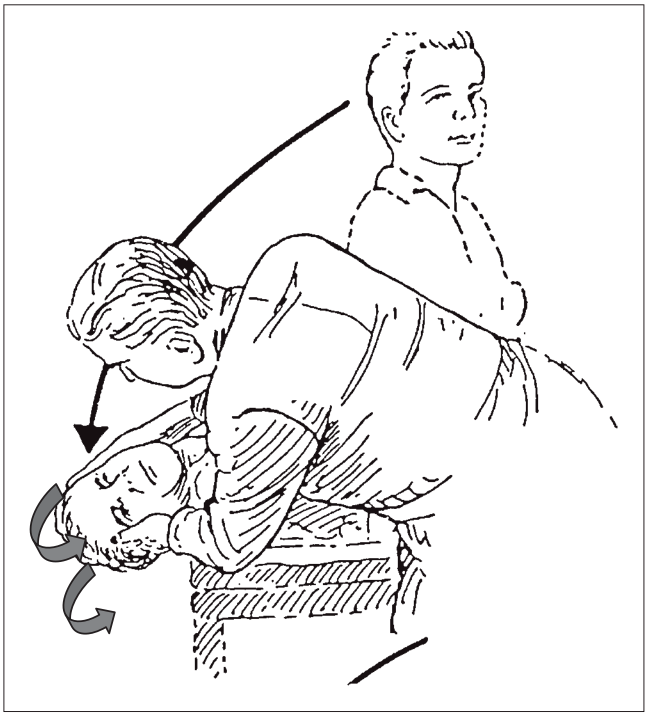

Figure 14.7 The Dix–Hallpike manoeuvre for diagnosing benign paroxysmal positional vertigo when it affects the posterior semicircular canal (p-BPPV). (From Baloh & Honrubia 2001, with permission.)

The Dix–Hallpike manoeuvre is a valuable test in such patients and can distinguish between the peripheral nystagmus of BPPV, central positional nystagmus and atypical positional nystagmus (Fig. 14.7):

- Seat the patient on a couch so that when supine, his/her head extends over the end of the couch.
- Ask the patient to remove spectacles; warn them they may feel intensely dizzy with the test.
- Keep the eyes open and maintain gaze on the examiner's forehead. (Remove stethoscope – it can fly around.)
- The patient's head is turned 30–45° towards the examiner and moved rapidly into the lying position with the head hanging 30° over the back of the couch. In this way the posterior semicircular canal of the undermost ear is moved directly through its plane of orientation. the patient's eyes are observed for nystagmus for up to 1 min.
- The manoeuvre is carried out with one and then the other ear undermost.

For the supine roll manoeuvre, the patient is seated on the couch with their legs outstretched (Fig. 14.8). Holding their head, the examiner lays the patient straight back on the couch looking for horizontal nystagmus. Once supine, the patient's head is turned towards the right side through 90° around the longitudinal *z*-axis. Typically, the induced nystagmus of horizontal canal BPPV (h-BPPV) beats towards the undermost ear (geotropic), and is more prolonged than that of posterior canal BPPV (p-BPPV). The nystagmus and associated vertigo is allowed to settle. The patient's head is then turned 180° to the left around the same longitudinal *z*-axis. Any nystagmus caused by horizontal canalolithiasis reverses, e.g. right-beating nystagmus becomes left-beating, i.e. it remains geotropic and is direction changing (see below).

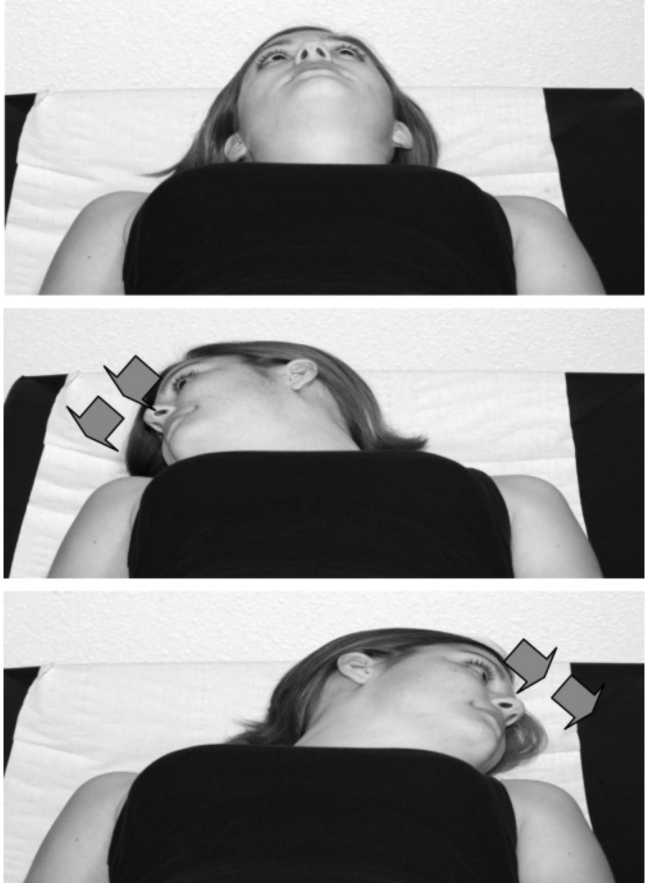

Figure 14.8 The supine roll manoeuvre for horizontal benign paroxysmal positional vertigo (BPPV). (From Bertholon *et al.* 2006, with permission.)

To check for h-BPPV in the opposite ear, repeat the manoeuvre, starting by moving the patient's head from the straight back position through 90° to the left side, waiting for the nystagmus to appear and disappear, and then rolling the head through 180° to the right. Laterality of h-BPPV is assigned to the side to which the more marked horizontal nystagmus occurs.

Central positional nystagmus

In central positional nystagmus, sometimes seen in multiple sclerosis, Arnold–Chiari malformations, posterior fossa lesions or cerebellar vascular disease, typically there is no latency to the onset of nystagmus, frequently little vertigo and no adaptation or fatigability. The direction of nystagmus may be towards the uppermost ear or may be vertical. Positional nystagmus may be the only sign of posterior fossa pathology.

Congenital nystagmus

The patient with congenital nystagmus rarely complains of oscillopsia, but does have a central movement abnormality. The nystagmus is in the horizontal plane and may change direction. There is a null point, which is often the eye position the patient adopts for reading; the slow phase is dysmorphic and may be exponential as demonstrated on the ENG. Characteristically, there is reversal of OKN, i.e. the slow phase of OKN does not match the direction of drum rotation (Fig. 14.6).

Periodic alternating nystagmus

This is a rare sign of cerebellar and caudal brainstem lesions. Periodic alternating nystagmus changes direction with a change of head or eye position. Cycle length varies from 1 to 6 min with null periods of 2–20 s. The precise site of the lesion is unknown.

Torsional nystagmus

This nystagmus is a rotation of the eye, beating around the visual axis, and can be quite hard to detect. It is best seen by observing the small blood vessels within the conjunctiva. The direction of the beating nystagmus is better specified in right–left and rotational terms, to avoid confusion; e.g. right → left, clockwise nystagmus, as noted by the examiner facing the patient. This is usually caused by a lesion of the contralateral vestibular nuclei, e.g. Wallenberg's syndrome (Chapter 4).

Pendular nystagmus

This is seen either with long-standing or congenital visual defects – when it is not associated with balance symptoms – or it can develop weeks to months after structural brainstem disease. In the latter, patients usually show cerebellar or pyramidal features and describe oscillopsia, largely unchanged by head movements. 'Jelly' nystagmus is a fine pendular nystagmus seen occasionally with MS brainstem lesions.

Halmagyi headthrust test

Halmagyi and Curthoys described a simple, reliable bedside test of horizontal semicircular canal function in 1988 (Fig. 14.9). The sign is correlated with unilateral canal paresis. The patient is seated upright with gaze fixed on a target 3 m away. The examiner sits in front of the patient and instructs them to keep looking at the target while the examiner turns their head quickly from one side and back to the midline and then to the other.

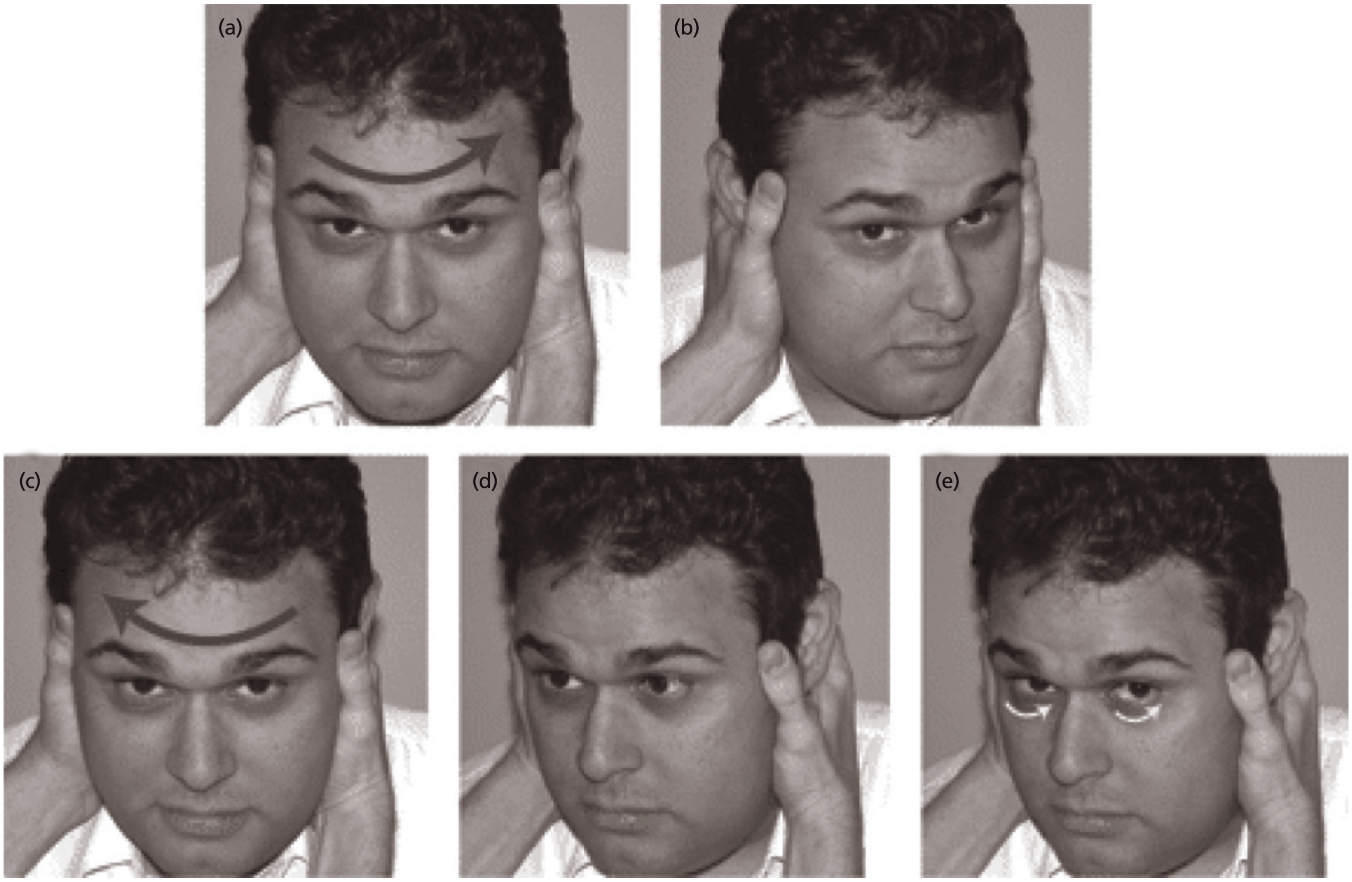

Figure 14.9 Halmagyi's headthrust test, which identifies right horizontal semi-circular canal paresis. (From Schubert *et al.* 2004, with permission.)

When the head is rapidly rotated towards the side of the lesion, oppositely directed, compensatory, re-fixation saccades are seen. With a right horizontal semicircular canal paresis, when the patient is rotated to the right, leftward saccades are seen. When the head was rotated towards the left, the patient makes smooth compensatory conjugate eye movements.

This phenomenon is in keeping with Ewald's observation that in the horizontal semicircular canal, endolymph movement towards the cupula, i.e. ampullo-petal, results in more vigorous nystagmus than when endolymph movement is ampullo-fugal. This asymmetry can perhaps be best understood when the discharge rate of primary vestibular afferents is considered: this rate can be driven to zero with rapid ampullo-fugal flow-producing accelerations, but the discharge rate with ampullo-petal flow-producing accelerations cannot be saturated. Halmagyi's head-thrust test is of the high frequency vestibulo-ocular reflex and tends to be positive with more severe peripheral vestibular deficits. Abnormalities are also seen with non-organic problems.

Tests of stance and gait

In contrast to the complexity of some of the observations of eye movements, these tests are simple to interpret and yet remain of value.

Romberg's test

Romberg described this test in 1846 in patients with dorsal column loss following tabes dorsalis. The test is positive if there is increased body sway when the eyes are closed and the patient stands with the feet close together. The principle behind the test is that balance is maintained with minimal physiological sway when all three sensory inputs are functioning, i.e. vision, vestibular input and proprioceptive input. With the loss of one or more of these inputs, there is increased physiological sway. Unsteadiness on Romberg testing can also occur with acute vestibular deficits and with cerebellar disease, although in the latter, the effects of eye closure theoretically should not affect sway.

Unterberger's test

In the 1930s, Unterberger described the tendency for vestibular imbalance to cause patients to turn when walking. The test identifies that the direction of turning in patients with unilateral vestibular deficits coincides with the direction of past-pointing and falling, i.e. in the direction of the slow component of nystagmus. The test is performed by asking the patient to stand with arms extended and thumbs raised, to close their eyes and asked to march on the spot for about 50 steps. The angle of rotation and any forward or backward movements are recorded. However, there is often marked variability in the rotation angle in the same subject on repeated testing. Unterberger's test should be interpreted in the context of other vestibular tests, rather than in isolation. Non-organic problems frequently produce apparent abnormalities.

Gait test

This is a 5-m walk, first with the eyes open and then with the eyes closed, with the examiner close alongside for safety. The patient should walk at normal speed towards a fixed target. As with Unterberger's test, patients with recent unilateral vestibular hypofunction tend to deviate towards the side of the lesion.

Tandem gait test

Tandem gait testing is useful for assessing vestibulo-spinal function. When performed with the eyes open, tandem walking is primarily a test of cerebellar function because vision compensates for chronic vestibular and proprioceptive deficits. Tandem walking with eyes closed is a good test of vestibular function as long as cerebellar and proprioceptive functions remain intact: ask the patient to take 10 heel–toe steps at a comfortable speed, starting with feet in the tandem (heel to toe) position and arms folded against the chest. Most normal subjects can manage 10 accurate tandem steps in three trials.

Commonly used vestibular investigations

The three approaches to physiological investigation of the vestibular system are:

- Recording eye movements
- Measurements of postural changes; and
- Measurements of the caloric responses (to hot and cold thermal irrigations) of the semicircular canals.

Eye movements are well-suited to measurement. Ocular motility is restricted to the rotations of the globe, the eye muscles moving the globe against an unchanging resistance. Different types of eye movement can be distinguished by their physiological properties. Direct observation of eye movements is useful, while recording techniques such as electronystagmography, video-oculography (VOG) and spiral coil recordings allow detailed evaluation and provide a permanent record for comparative purposes.

Electronystagmography

Electronystagmography (ENG) is the simplest and most readily available system for recording eye movements. A recording electrode placed laterally to the eye becomes increasingly positive as the eye turns towards it and negative when the eye turns away. The voltage change represents the change in eye position. Only small angular movements are involved in nystagmus and thus the relationship between voltage change and eye movement is virtually linear within small degrees of arc. The polarity of the recording is arranged so that a deflection of the eye to the left causes a downward deflection of the pen and vice versa. The sensitivity of ENG is such that it can record consistently eye rotations of 0.5°. This sensitivity is actually less than that of direct visual inspection – approximately 0.1°.

The plane of the recording electrodes is in the plane of recorded eye movement, i.e. electrodes attached medially and laterally to the eye record horizontal components of eye movement, whereas those attached above and below record vertical components. A single-channel ENG machine summates horizontal movements of both eyes from bi-temporal recordings on to the same trace. A two-channel ENG records movement of each eye separately; four-channel ENG can record simultaneously vertical and horizontal movements. Paper speed at 10 mm/s is used, although when saccadic accuracy and velocity are measured, 100 mm/s or even faster speeds may be necessary. Calibration is such that a standard angle of eye deviation produces a defined amplitude of pen deflection – commonly 10 mm of pen deflection for each 10° of eye movement. A detailed standardized protocol is essential.

Clinical relevance of ENG

The main value of ENG recordings is that some patients have demonstrable nystagmus only when optic fixation is removed.

- *Peripheral vestibular disorders*: unless acute, these are unlikely to be associated with nystagmus in the presence of optic fixation but nystagmus can be revealed if fixation is removed, i.e. with the use of the Frenzel's glasses or video-nystagmoscopy, and is of increased amplitude in darkness. Nystagmus is unidirectional with the largest amplitude on horizontal gaze towards the direction of the fast component (Fig. 14.10).
- *Vestibular nuclei lesions*: in darkness the amplitude of nystagmus may hardly alter but the velocity of the slow phase may be decreased. Often the nystagmus is bi-directional.
- *Cerebellar lesions*: these may be associated with pathological square waves with duration <200 ms. With direct current ENG recordings a characteristic abnormality of cerebellar pathology is the failure to maintain lateral gaze, with a slow drifting movement of the eyes towards the midline. Rebound nystagmus can also be seen, but when cerebellar, it is transient and persists for a maximum of 20 s. Patients with cerebellar disease may have difficulties in executing commands for saccadic movement. When asked to turn their gaze laterally quickly, they overshoot the target.

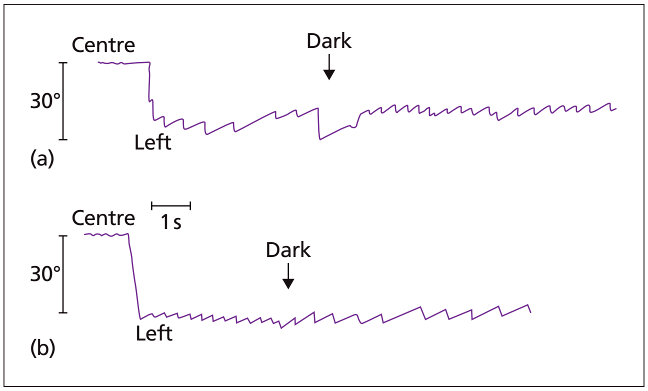

Figure 14.10 Electronystagmography (ENG): effect of removing optical fixation. ENG records from patients with: (a) a peripheral vestibular deficit: spontaneous nystagmus on gaze right is enhanced in the absence of optic fixation; (b) a gaze evoked nystagmus: nystagmus decreases in frequency and slow component velocity in the absence of optic fixation. (From Luxon 1988, with permission.)

Rotary chair testing

Rotary chair testing allows measurement and recording of eye movement responses to precise vestibular stimuli (Fig. 14.11). This can be of immense clinical value. The VOR provides a simple example of a reflex arc comprising the vestibular sense organ, the primary, secondary and tertiary vestibular neurones and the effector organs, the oculomotor muscles. Angular acceleration in the plane of the semicircular canal leads to endolymph displacement in a direction opposite to that of rotation. As a consequence, the cupula of that canal deviates in the same direction as the endolymph, resulting in a change of vestibular tonus, an excitatory stimulus being matched by an inhibitory stimulus from the opposite side. As a result there is an impact on the pair of muscles producing the compensatory eye movement, i.e. excitation of the antagonist muscle and disinhibition of the agonist muscle. An acceleration to the right in the plane of the horizontal canal will produce deviation of the eyes to the left.

Vestibulo-ocular reflexes act during all natural head movements, coordinating with visual and cervico-ocular reflexes to provide both the most appropriate eye position and eye stability during head movements. Vestibular nystagmus is suppressed by visual fixation, but it may be elicited with Frenzel's glasses or video-oculography (VOG).

Types of rotary chair stimuli

Impulsive (*step velocity*) *stimuli*. Constant velocities such as 40, 60, 80 or 120°/s are attained with an abrupt acceleration of the chair, brought to constant velocity within 1 s. This constant velocity is maintained for up to 2 min while the nystagmic response dies away. The chair is suddenly brought to rest with the same deceleration and the normal limits of nystagmus intensity are established with normal subjects. This provides a rapid assessment of gain (peak slow component velocity ÷ change in chair velocity) and the time constant (time for the slow

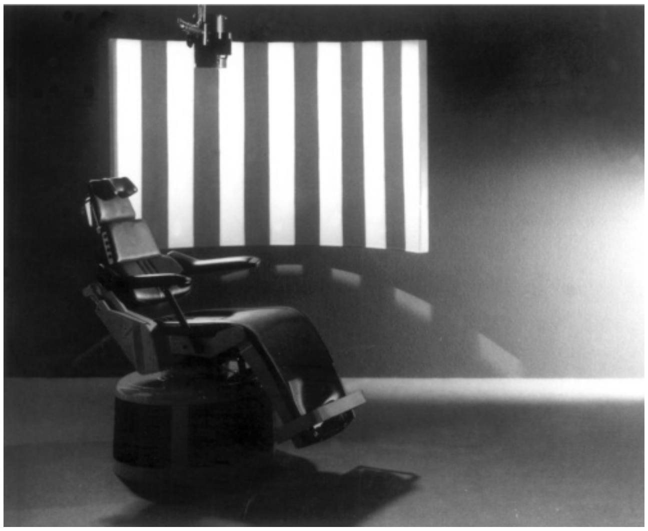

Figure 14.11 Optokinetic stimulation. (From Davies 2004, with permission.)

component velocity to fall to 37% of its initial value) of the canal reflex.

Sinusoidal stimuli. To and fro swinging movements of the chair around its vertical axis are programmed with variable stimulus parameters, e.g. frequency and amplitude. The threshold for recordable nystagmus, defined as the angular acceleration maintained for 20 s that will produce nystagmus is $0.15°/s^2$ in the absence of optic fixation. With optic fixation the nystagmus threshold is raised and is normally about $1°/s^2$.

Rotational testing is normally performed in darkness but sinusoidal rotation can also be performed with the eyes focused on a target that revolves with the patient, around the vertical axis. This has the purpose of allowing VOR suppression to be assessed. This is an important test of central vestibular function, as visual suppression of the VOR is mediated by central vestibular pathways.

Clinical relevance of rotary chair testing

Rotational stimuli can be used to demonstrate a directional preponderance as determined by the ratio of the duration of nystagmus following the onset of acceleration to that following deceleration. A disadvantage is that both labyrinths are tested simultaneously; unilateral dysfunction may be difficult to identify if the lesion is old and the patient is well-compensated. Rotary chair testing is of particular value in the following situations:

- A negative caloric test, where high frequency oscillation/high intensity acceleration may give evidence of some residual vestibular function;
- Investigation of visuo-vestibular interactions – when failure to suppress the vestibulo-ocular reflex with fixation is evidence of central vestibular dysfunction.

With computerized analysis of responses to rotary chair testing, results can be depicted in a quadrantic fashion following the sequence of start–stop stimuli in a clockwise then anticlockwise direction. These displays include a mathematical computation of directional preponderance using slow phase velocity and/or durational criteria. Multivariate analysis of sinusoidal harmonic accelerations, asymptotic gain and the time constant have demonstrated a minimal misclassification rate when comparing normal people with patients with total canal paresis.

Video-oculography

Video-oculography is a technique for observing and recording eye movements. An infra-red camera is mounted within goggles and connected to a video monitor. Observation and recordings of the eye movements in the absence of optic fixation can be made in response to a variety of stimuli. This technique is now a standard investigative tool in many departments. A test protocol can be performed which allows videotape recording of the following:

- Spontaneous nystagmus;
- Head-shaking nystagmus;
- Passive head tilt;
- Head rotation through 180°

VOG is valuable for identifying and classifying peripheral vestibular lesions.

Caloric testing

This is the most widely available of all vestibular tests and for many otologists is the cornerstone of vestibular diagnosis. Its great value is that it allows each labyrinth to be tested separately. The stimulus is easy to apply and involves inexpensive methodology. The test remains unrivalled as a method of demonstrating a peripheral vestibular deficit.

Principles of caloric testing

After irrigation of the ear with water 7°C below (30°), and then 7°C above (44°) body temperature, a gradient is set up between the external auditory meatus (EAM) and the two limbs of the horizontal canal. This is by virtue of the position of the patient, whose head is at 30° to the horizontal on the couch. This means that the horizontal semicircular canal becomes vertical and the temperature gradient crosses from one limb of the canal to the other. It is believed that the endolymph circulates because of the difference in the specific gravity on the two sides of the canal. With warm water, there is ampullo-petal flow, with cupular deflection towards the utricle, resulting in activation of the VOR, a sensation of vertigo and horizontal nystagmus directed towards the stimulated ear. There remain some questions regarding this convection theory, because caloric nystagmus under microgravity conditions still occurs, e.g. in space.

The Hallpike–Fitzgerald bithermal caloric test has been available to clinicians for more than 60 years. Each ear is irrigated in turn for 40 s first with water at 30°C and then at 44°C. Inspection of the tympanic membrane after warm irrigation confirms an adequate stimulus if a red flush is seen on the membrane.

Direct observation of the eyes allows the endpoint of the nystagmic reaction to be measured. During the procedure, the patient is asked to direct gaze on a fixation point on the ceiling, making the endpoint easier to determine. At this point the lights are switched off and the eyes observed with Frenzel's glasses or infrared gun. Under normal situations the vestibular nystagmus would be expected to reappear. The endpoints of each test are graphically recorded.

Quantitative analysis

Normally, nystagmus ceases 90–140 s after onset of irrigation and returns for up to a further 60 s after removal of optic fixation. Two patterns may appear, either separately or in combination.

1 *Total canal paresis* This is the complete loss of labyrinthine function in one ear, seen when there is a total absence of nystagmus following both 30° and 44° irrigations, even in the absence of optic fixation. Ideally, the test should be repeated using cold water at 20° for 60 seconds to confirm the result. It may reflect an ipsilateral lesion of the labyrinth, VIIIth nerve or brainstem vestibular nuclei, and confirms unilateral vestibular hypofunction (Fig. 14.12).

2 *Directional preponderance* This occurs when the responses to thermal irrigations produce an excess of nystagmus in one direction, i.e. towards either the right or the left. This indicates imbalance of vestibular tone arriving at the oculomotor nuclei, a result of either a peripheral vestibular lesion (labyrinth, VIIIth nerve or nuclei) or from a central vestibular lesion, within the cerebellum or brainstem. With more pronounced degrees of vestibular tone imbalance, spontaneous nystagmus makes its appearance.

Figures for duration of nystagmic responses in seconds can be entered into the Jongkees formula, which calculates a percentage figure expressing either the degree of canal paresis or directional preponderance:

$$\text{Canal paresis }(\%) = (\text{R}30° + \text{R}44°) - (\text{L}30° + \text{L}44°)$$
$$(\text{R}30° + \text{R}44° + \text{L}30° + \text{L}44°) \times 100$$
$$\text{Directional preponderance }(\%) = (\text{L}30° + \text{R}44°) - (\text{L}44° + \text{L}30°)$$
$$(\text{L}30° + \text{R}44° + \text{L}44° + \text{R}30°) \times 100$$

Another measurement, the optic fixation index (OFI) is calculated by dividing the summed durations in the light by the summed durations in the dark. If there is no enhancement in the absence of optic fixation, i.e. the OFI is 1.0, the cause may be central – within the cerebellum or vestibulo-cerebellar tracts. Bilateral decreased caloric responses indicate either bilateral vestibular impairment, or vestibular habituation. The latter is seen in acrobats, ice skaters and ballet dancers (OFI <0.5).

ENG caloric recordings

There are both advantages and disadvantages using ENG for caloric testing. The technique provides a permanent record of the caloric response in both light and dark and allows individual features of the nystagmus, i.e. slow component velocity, interbeat frequency and the amplitude, to be analysed. The comparative disadvantages when compared with the Fitzgerald–Hallpike technique are:

- It is difficult to detect the endpoint of nystagmus as accurately as with direct vision, but hard copy data are recorded.
- Recording caloric nystagmus with the eyes closed is compromised by Bell's phenomenon, i.e. the eyes rolling upwards with lid closure, but using VOG, the eyes remain open.
- Other nystagmic components in the vertical direction are missed, e.g. torsional nystagmus; this can be seen with VOG calorics.

A direct comparison has been made between the maximum slow component velocity and the durations of the four caloric responses in normal subjects (Fig. 14.12). The durations were relatively stable as a parameter, whereas the slow component velocities showed considerable variations in some subjects. Further analysis showed that the test–retest unreliability of the slow component velocity was unacceptably high. Direct visual observation has the advantage that the endpoint of the nystagmus can be estimated more reliably both with and without optic fixation, but does rely on an experienced observer.

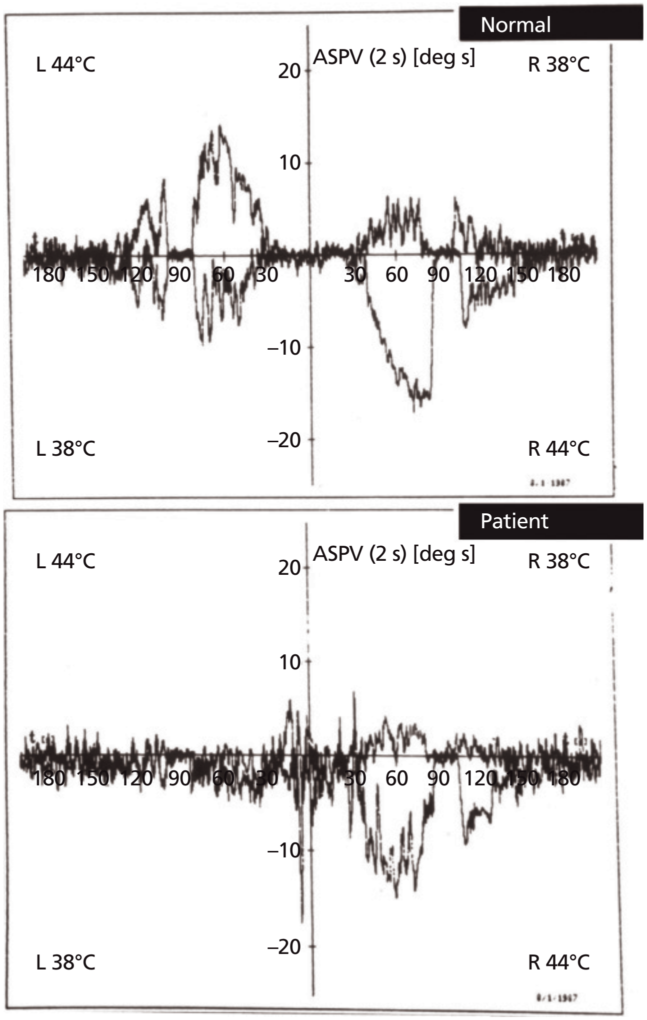

Figure 14.12 Four-quadrant display of caloric irrigations. A graphic record of a set of normal responses to caloric irrigation in the upper four-quadrant display; the lower four-quadrant display shows a partial canal paresis on the left. (From Davies 2004, with permission.)

Closed-circuit and air caloric testing

Some commercial caloric testing kits use closed irrigation systems to warm and cool the EAM or use air instead of water. The problem with the former is that the tube in which the water flows does not fully occupy the EAM, thus reducing the effectiveness of the stimulus. With the latter, the specific heat of air is much lower than that of water; this means a greater temperature differential is required to effect the same temperature gradient across the labyrinth, i.e. a hot air stimulus of 50°C which needs to be delivered for 60 s will give an equivalent to the 44°C water stimulus. This may be unpleasant and tolerated poorly. Air calorics are generally regarded as less reliable than traditional hot and cold water calorics.

Clinical value of caloric testing

Caloric testing is an essential part of the evaluation of the vestibular system. It tests each labyrinth individually and does not require any sophisticated instruments if water irrigation is used. The quantification and normal values of the measured parameters of the caloric induced nystagmus have been well-established. The Jongkees formula is a validated measure, to calculate both canal paresis and directional preponderance. However, caloric test results do not correlate with the degree of dizziness or vertigo and are thus not a measure of discomfort or distress caused by these physiological abnormalities. Also, if a patient has a degree of directional preponderance or canal paresis, this may reflect a vestibular insult at some time even in the distant past, and one from which clinical recovery would be usual. This can have particular relevance in legal claims.

Posturography

It is well known that alterations in vestibular function can profoundly affect posture. Postural control is a vital physiological function if we are to continue any daily activity and is determined by a complex sensorimotor feedback system dependent on a variety of coordinated reflexes. Only in the last two decades have objective measures of vestibulo-spinal postural reflexes been possible. Clinically, the Romberg test has been used to assess postural stability. During normal standing, the body is in continuous motion, i.e. physiological sway, even when attempting to remain still. This is an active process, whereby any loss of balance is compensated by movement of the body's centre of gravity (CoG). These movements result in visually detectable sway movements that maintain the CoG vertically over the base of support.

Static force-plate posturography was an early method of measuring body sway. A typical force-plate consists of a flat rigid surface supported on three or more points by independent force-measuring devices. As the patient stands on the plate, the vertical forces recorded by the measuring devices are used to calculate the position of the centre of the vertical forces exerted on the force-plate over time. With the height and weight of the patient, a computer model of body dynamics can be used to derive the CoG sway angle over time.

Moving platform posturography has been designed to overcome the limitations of the static force platform by controlling the relative contributions of visual, somato-sensory and vestibular input. Commercially available platforms calculate body sway based on changes in horizontally (sheer) and vertically oriented (torque) strain gauges mounted under the support surface. The Equitest platform (Fig. 14.13) utilizes the concept of sway-referencing, i.e. both the support surface and the visual surround can be modulated in phase with the patient's own body sway.

This coupling of either the platform or visual surround to the sway of the subject allows the angle between the foot and the lower leg to be maintained at a constant value, thus minimizing somatosensory input with visual input remaining constant despite the subject's sway, respectively.

Six conditions are used in the sensory organization testing and analysis of the sway scores allowing each of the three principal balance sensors to be isolated and comparisons made to assess sensory preference. The sensory organization test battery identifies abnormal patterns of postural control, not adequately assessed by studies of the vestibulo-ocular reflex alone and examines the utilization and integration of visual and somatosensory input with vestibular information, especially under conditions of sensory conflict (Fig. 14.14).

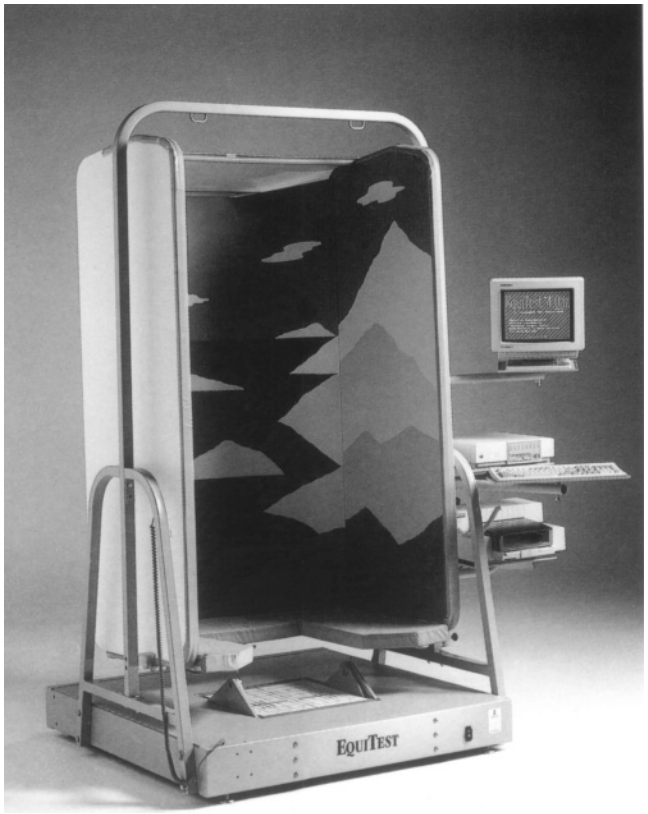

Figure 14.13 The Equitest balance platform. Posturography with sway referencing of both the support surface and the visual surround. (From Davies 2004, with permission.)

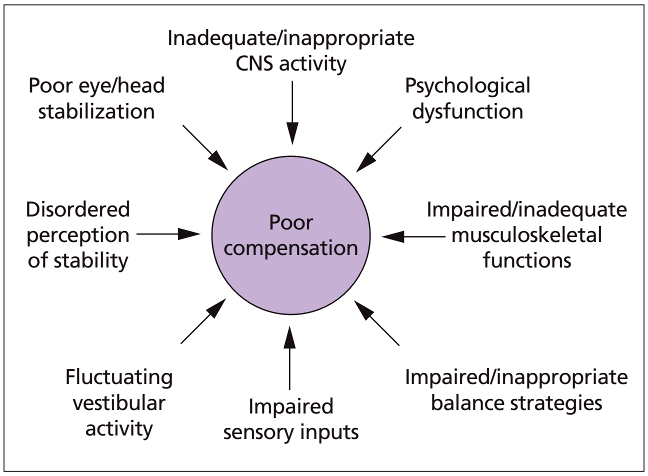
Inadequate/inappropriate CNS activity
Poor eye/head stabilization
Psychological dysfunction
Disordered perception of stability
Poor compensation
Impaired/inadequate musculoskeletal functions
Fluctuating vestibular activity
Impaired sensory inputs
Impaired/inappropriate balance strategies

Figure 14.14 Factors predisposing to vestibular decompensation. (From Luxon 1997, with permission.)

The moving platform has been shown to be of great benefit in rehabilitation but of limited value as a diagnostic test.

Limitations of vestibular tests

A major disadvantage of all types of vestibular test is that normative data are not universal and therefore, each data set needs to be collected for each laboratory before it can be used. The equipment for the rotary chair and posturography is expensive and requires space and dark rooms. There is no gold standard for vestibular testing and the results of all the tests in the battery must be used in conjunction with the clinical picture. A further limitation is that whilst vestibular testing may show an abnormality, not infrequently the site of the lesion cannot be indicated with certainty.

Clinical disorders

The major peripheral vestibular syndromes are described here.

Vestibular neuritis

Vestibular neuritis (VN) is one of the three most common causes of acute vertigo. It can be thought of as an acute unilateral vestibular paresis and has variously been known as vestibular neuronitis, vestibular neuro-labyrinthitis or acute vestibulopathy. The syndrome is also often referred to as labyrinthitis, a misnomer as there is neither hearing loss nor tinnitus. VN is a well-recognized syndrome rather than a clearly defined clinico-pathological entity, characterized by:

- Acute rotary vertigo (sense of movement away from the side of the lesion);
- Blurred vision/oscillopsia (fast phase of nystagmus directed contralaterally);
- Postural imbalance (positive Romberg and falling towards the side of lesion); and
- Nausea and vomiting.

The onset of VN is typically sudden, without prelude and the degree of real distress out of proportion to the seriousness of the condition. Resolution is usual within a matter of weeks. The clinical picture may be sufficiently clear for further investigation to be unnecessary. For confirmation of diagnosis, unilateral peripheral vestibular hypofunction needs to be identified either at the bedside (Halmagyi headthrust test) or in the balance clinic (using a caloric test). The caloric test shows ipsilateral hyporesponsiveness or non-responsiveness, a sign of horizontal semicircular canal dysfunction.

Aetiology

The possible aetiologies of vestibular neuritis include viral and vascular insults, although in practice a cause is rarely established. Pointers toward a viral aetiology or viral re-activation are:

- Frequency of preceding upper respiratory tract infection;
- Postmortem studies – cell degeneration of one or more vestibular nerve trunks; and
- Demonstration of latent herpes simplex virus type I in human vestibular ganglia.

VN is thought to have a predilection for the superior division of the vestibular nerve, but the dysfunction may equally involve the sensory hair cells of the vestibular end organ and hence the term ‘neuritis’ is used. Similar presentations can be caused by:

- Multiple sclerosis when a plaque is within the VIIIth nerve root entry zone; and
- Cerebellar vascular disease (see below).

Clinical assessment

Nystagmus is caused by an imbalance between afferent vestibular tone from the two labyrinths. Decrease in afferent activity from the affected ear is integrated with unaltered activity from the normal ear to produce the vestibular, or slow, phase of the nystagmus which is directed towards the affected ear. The fast or saccadic phase, which re-fixes the target on the fovea is towards the unaffected labyrinth. The acute nystagmus is predominantly horizontal-torsional. The reason for this is considered to be the net effect of the three unopposed semicircular canals, i.e. horizontal, posterior and anterior canals. Activity of the two vertical canals cancels out the vertical effect – the posterior canal tending to drive the eyes upwards and the anterior canal tending to drive the eyes downward. The patient senses movement across the retina only during the slow phase of nystagmus and because of the inverting effect of the lens, the sense of movement appears to be in the same direction as the fast phase of the nystagmus.

The postural reactions initiated by the vestibulo-spinal reflexes are usually opposite to the direction of vertigo. This results in Romberg’s and Unterberger’s tests being directed towards the side of the lesion. The patient’s subjective sense of straight ahead and perceived visual vertical represents perceptual consequences of vestibular tone imbalance in yaw and roll planes.

Neuro-otological investigations

If investigation is necessary, video-nystagmography confirms a spontaneous vestibular nystagmus directed towards the unaffected ear that increases with removal of optic fixation. With gaze towards the unaffected side (i.e. in the direction of the fast phase), the nystagmus increases in frequency and amplitude. On gaze towards the affected ear, the nystagmus decreases in amplitude and frequency. This effect on the nystagmus by direction of gaze (Alexander’s law) may be first degree, second degree or third degree. This depends upon whether it is present – toward the side of the lesion (first degree), looking straight ahead (second degree) or away from the side of lesion (third degree).

Course

Throughout the acute phase (1–3 days), patients feel intensely unwell and tend to stay in bed. All head movements exacerbate vertigo, nausea and imbalance. After some 3 days, the spontaneous nystagmus is usually suppressed by optic fixation in the primary position but can still be detected with gaze towards the unaffected ear, and in the absence of optic fixation, e.g. with

Table 14.9 Features of cerebellar infarction presenting as apparent vestibular neuritis. (From Lee *et al*. 2006, with permission.)

Findings in 24 patients with mPICA cerebellar infarction and PVN	
Halmagyi headthrust test	Normal
[1]Spontaneous nystagmus*	15
[1]Gaze-evoked nystagmus	24
Unidirectional†	7
Bidirectional:	
direction changing‡	13
direction unchanging	4
[1]Asymmetric smooth pursuit	6
[1]Asymmetric OKN	4
[1]Canal paresis	None

mPICA, medial branch of the posterior inferior cerebellar artery; OKN, optokinetic nystagmus; PVN, pseudovestibular neuritis.

[1] Performed using electro-nystagmography (ENG) 1 week after onset of vertigo.

* Beating towards lesion side.

† Only on gaze towards lesion side.

‡ Maximal to lesion side.

Frenzel's glasses. After 1–6 weeks, most patients become asymptomatic, experiencing dizziness only with rapid head movements. Some 50–70% show complete recovery as assessed by caloric testing.

Differential diagnosis of vestibular neuritis

When a patient presents acutely with symptoms of severe persistent isolated vertigo with imbalance, the distinct likelihood is that VN is the cause. However, the possibility of cerebellar infarction must also be considered. Features typical of VN can be the sole manifestation of the cerebellar infarction (Table 14.9). The territory most commonly involved is supplied by the medial branch of the posterior inferior cerebellar artery (mPICA). The term pseudovestibular neuritis (PVN) for isolated vertigo of cerebellar origin has also been coined. Magnetic resonance brain imaging may be necessary to distinguish between the two conditions and with the tendency towards defensive practice, imaging is becoming hard to avoid.

Benign paroxysmal positional vertigo

Barany first described benign positional vertigo in 1921, recognizing it as a lesion of the vestibular end organ involving the otolith, but not until 1952 was it redefined and renamed as benign paroxysmal positional vertigo (BPPV). BPPV, when it affects the posterior semicircular canal (p-BPPV) is characterized by brief attacks of rotary vertigo and concomitant, positioning (aka positional), rotary-vertical/geotropic nystagmus, elicited by changes in head position in the plane of the posterior semicircular canal.

Incidence of BPPV

BPPV is probably the most common cause of vertigo, particularly in the elderly. One survey reported that by the age of 70, 30% of the population had experienced BPPV at least once. However, patients of any age can be affected, the overall mean age of onset being in the fifth decade, with a peak incidence around the mid-sixties, women outnumbering men by nearly 2 : 1. There is a slight female predominance in a presumed post-viral group, a higher female : male ratio in an idiopathic group and no sex predominance in a post-traumatic group. The peak age of onset is the fourth decade for the presumed post-viral group, the sixth decade for the idiopathic and an even distribution through the second to sixth decades in the post-traumatic group.

Posterior semicircular canal BPPV

The diagnosis of p-BPPV is made by a typical history of severe vertigo lasting less than 1 min, triggered by specific head movements, e.g. lying back or rolling over in bed, extending the neck to change a light bulb or pick a book from a high shelf, or bending forwards to wash the hair. It is thought to be caused by an accumulation of otolith debris which has become displaced from the otolith membrane of the utricle and has settled as a bolus of crystals in the most gravity-dependent part of the inner ear, the posterior semicircular canal. The bolus is heavier than the surrounding endolymph and gravitates to the most dependent part of the canal during changes in head position (canalolithiasis; Fig. 14.15).

Acting like a plunger, the bolus exerts an ampullo-fugal pull on the cupula, triggering the BPPV attack. The diagnosis is confirmed by characteristic nystagmus on Dix–Hallpike manoeuvre, i.e. ampullo-fugal stimulation of the cupula of the posterior semicircular canal causes excitation of the ipsilateral superior oblique and the contralateral inferior rectus muscle, causing both eyes to move downward (Fig. 14.16). The refixating fast phase of the nystagmus is upbeat and is combined with a torsional component because of the different angles of insertion of the oblique and rectus muscles.

The diagnostic criteria for nystagmus typical of p-BPPV are:

- *Latency*: vertigo and nystagmus commence between several and 20 s after the head-hanging position is reached;
- *Duration*: nystagmus gradually reduces after 10–40 s, before it disappears;
- *Rotary-vertical (upbeat) nystagmus* is present with the fast phase beating toward the undermost ear (geotropic);
- *Reversal*: on returning to the upright position the vertigo and nystagmus may reoccur less violently in the opposite direction;
- *Fatiguability*: on repeating the manoeuvre, the vertigo and nystagmus lessen.

The initial Dix–Hallpike test should be directed toward the ear assumed to be affected, as the nystagmus will become less evident on subsequent manoeuvres, demonstrating fatiguability.

Horizontal canal BPPV

Between 5% and 20% of patients with BPPV are thought to suffer from horizontal canalolithiasis (h-BPPV). It may be combined with p-BPPV of the same ear or represent a transition from p-BPPV to h-BPPV as a result of a therapeutic manoeuvre. These

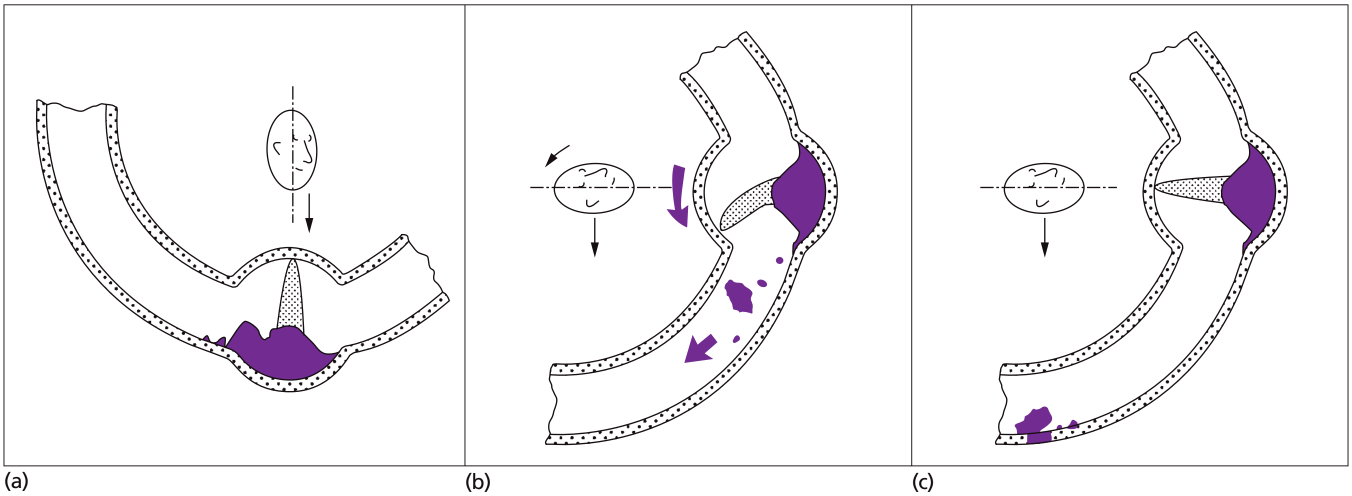

Figure 14.15 Canalolithiasis. Schematic representation of a free-floating 'heavy clot' of otoconial debris acting like a plunger on the endolymph and cupula of the posterior semicircular canal. (a) Normal upright position. (b) Head is turned and rapidly positioned to the side, in the plane of the posterior SCC. The clot gravitates downwards because of its heavier specific gravity, deflecting the cupula in an ampullo-fugal direction. (c) When the clot has gravitated to the lowest curvature of the posterior canal, vertigo and nystagmus subside because the cupula resumes its normal resting position. (From Brandt & Steddin, 1993 with permission.)

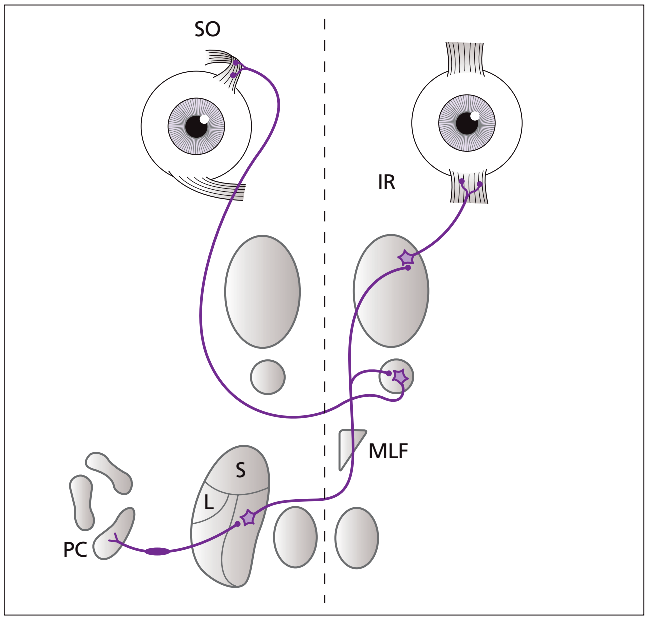

Figure 14.16 Excitatory connections of the posterior canal. The activation of the hair cells of the posterior canal results in a torsional, upbeating nystagmus which reflects the excitatory connections of the posterior canal (PC) with ipsilateral superior oblique (SO) and contralateral inferior rectus (IR) muscles. MLF, medial longitudinal fasciculus; S, superior vestibular nucleus. (From Leigh & Zee 1991, with permission.)

two varieties of BPPV are thought to have similar aetiological bases. Symptomatically patients experience episodic vertigo when turning the head from side to side or on lying back in bed. When the Dix–Hallpike manoeuvre provokes a purely horizontal nystagmus, h-BPPV should be suspected. However, the Dix–Hallpike test is positive for horizontal nystagmus in only 80% of h-BPPV cases. The supine roll test is diagnostic of h-BPPV. When h-BPPV occurs as the result of loose otolith crystals in the canal itself, i.e. canalolithiasis, the nystagmus is geotropic – it beats towards the undermost ear.

Atypical h-BPPV

Atypical h-BPPV is caused by cupulolithiasis, i.e. otolith crystals are adherent to the cupula rather than remaining free-floating in the horizontal canal endolymph. This causes apogeotropic positional nystagmus – nystagmus in the direction opposite to rotation.

The diagnostic manoeuvres are the same for h-BPPV cupulolithiasis and h-BPPV canalolithiasis. The difference is that in cupulolithiasis the nystagmus is apogeotropic: with right h-BPPV due to cupulolithiasis, when the head is rolled to the right this will elicit left-beating nystagmus. This nystagmus is often quite prolonged, distressing and may take some 2 min to settle. The nystagmus depends on the assumed head position and not on the net angle of rotation.

Anterior canal BPPV

BPPV of the anterior canal (a-BPPV) is a rare variant, and poorly characterized. It sometimes occurs as an unwanted effect of a particle repositioning manoeuvre (see below) for p-BPPV, i.e. when the otolith debris is inadvertently redirected into the anterior canal from the common crus at the final stage of an Epley manoeuvre. One proposed model is that positional downbeating nystagmus can be caused by anterior semicircular canalithiasis, assuming central causes are excluded. This is because of the ampullo-fugal effects of anterior canal stimulation. Extrapolating to nystagmus induced by the Dix–Hallpike manoeuvre, any

Table 14.10 Distribution of types of benign paroxysmal positional vertigo (BPPV) in patients with positional vertigo/nystagmus. (After Bertholon *et al.* 2006.)

Source	*n* (%)	Posterior (%)	Horizontal		Anterior (%)	Others
			Geotropic (%)	Apogeotropic (%)		
Herdman *et al.* (1994)	77	63	1		12	24% undetermined
Honrubia *et al.* (1999)	292	93	6	9	4	0
Korres *et al.* (2004)	168	90	14		3	0
Nakayama & Epley (2005)	833	66	10		2	21%
Bertholon *et al.* (2006)	100	61	11	7	1	1% (posterior & horizontal BPPV) 3% (peripheral nystagmus) 12% (central nystagmus) 4% (peripheral & central)

downbeating nystagmus could be explained by anterior canalithiasis in the uppermost ear. However, the differential diagnosis of positional downbeating nystagmus must always include central involvement and hence brain imaging.

The frequency of the various varieties of BPPV is shown in Table 14.10.

Migraine-related dizziness

Migraine and vertigo are both common disorders and the possibility of a causal link between the two has been postulated for well over a century. The following conditions are generally understood to link symptoms of dizziness to migraine-like phenomena: basilar migraine; benign paroxysmal vertigo of childhood; benign recurrent vertigo. A plethora of names has been introduced to better define this link: migraine-associated dizziness, migraine-related vestibulopathy, migraine-related dizziness, vestibular migraine and migrainous vertigo. Questionnaires exist to simplify classification of migraine-related dizziness, but the cornerstones are to make an accurate diagnosis of migraine using established criteria (Chapter 11) and, in the absence of an alternative explanation, to classify migraine linked temporally with dizziness to migrainous vertigo. There remains some variation in opinion in this area.

Prevalence and definitions

The lifetime prevalence of vertigo, both vestibular and non-vestibular, is around 25%. Prevalence studies show that migraine affects at least 16% of the adult population at some time in their lives, with women having a higher prevalence than men. In a dizziness clinic, the prevalence of migraine is over 30%. Migraine is an episodic headache disorder associated with nausea and/or vomiting, photophobia, phonophobia and/or osmophobia and general irritability and is often exacerbated by movement.

To date, this link between migraine and dizziness has not been formally incorporated into International Headache Society (IHS) terminology, other than the acceptance that dizziness can be one of the aura symptoms of basilar migraine.

Basilar migraine

It is common experience that many patients with migrainous headaches describe dizziness, and occasionally vertigo, especially prior to the onset of headache. Basilar migraine, by IHS criteria, can only be diagnosed if attacks are accompanied by two or more of the following features:

- Visual symptoms in the temporal/nasal fields;
- Dysarthria;
- Vertigo;
- Tinnitus;
- Decreased hearing;
- Diplopia;
- Ataxia;
- Bilateral paraesthesiae; and
- Decreased level of consciousness.

Several studies have investigated links between dizziness and migraine. One found that in more than 150 dizzy patients, over 35% had a verifiable diagnosis of migraine; 88% had vertigo both with and between migraine attacks; 52% had criteria sufficient for basilar migraine; dizziness and/or vertigo could occur at any time during a migraine attack, i.e. as part of an aura or as a more general symptom, often head movement related; the initial dizziness coincided with the first migraine in 23%; and vestibular testing showed abnormalities: directional preponderance in 50% and canal paresis in 25%. There is an undoubted need for a clear agreed nomenclature linking dizziness to migraine.

Benign recurrent vertigo

Benign recurrent vertigo was first described in patients who had attacks of sudden intense vertigo, postural imbalance with or without nausea, spontaneous or positional nystagmus lasting several hours, but without headache. Because it is agreed that migraine is not exclusively a headache syndrome, such stereotyped attacks of vertigo with a timescale equivalent to migraine could be regarded as a migraine equivalent.

Ménière's disease

Ménière's disease, also known as endolymphatic hydrops, is an inner ear disorder characterized by prolonged attacks of vertigo, fluctuating hearing loss, tinnitus and aural fullness. To make a definite diagnosis American Academy of Otolaryngology 1995 criteria are commonly used. Nonetheless, monosymptomatic cochlear or vestibular variants are possible depending on whether the endolymphatic hydrops affects predominantly the auditory or vestibular part of the labyrinth, and with time these patients may develop the full disorder. This is a reminder to keep a watching brief on those patients whose initial symptoms do not match the full criteria.

The mechanism underlying the disorder is thought to be a failure of resorption of endolymph by the endolymphatic sac. This view is supported by EM studies, by the finding of peri-saccular fibrosis of the endolymphatic duct and by high resolution magnetic resonance imaging (MRI). With Ménière's cases, the endolymphatic duct can be visualized on MRI less often than in control subjects. This overaccumulation of endolymph leads to distortion of the membranous labyrinth, i.e. endolymphatic hydrops.

Ménière's disease can rarely be congenital, e.g. associated with Mondini dysplasia. It is usually acquired, e.g. after an evident inflammatory or traumatic insult to the labyrinth (when it is sometimes known as delayed endolymphatic hydrops), or idiopathic, when it occurs in about 21/100,000 of the population, presenting at 40–60 years of age. The endolymphatic hydrops starts in the helicotrema leading to ruptures of Reissner's membrane separating perilymph from the endolymph and accounting for the symptoms of fullness of the ear during an attack. With these periodic ruptures of Reissner's membrane there is endolymph discharge with a flux of potassium ions across the breached membrane (from 150 mmol/L in endolymph to 8 mmol/L in perilymph). This causes a temporary palsy of the vestibulocochlear nerve fibres located in the perilymph space. There is an initial excitation of the nerves leading to severe vertigo and an irritative nystagmus, i.e. beating towards the affected ear. Later, there is blockade of action potentials leading to inactivation of the axonal sodium channels and nystagmus (known as destructive nystgamus) beating toward the unaffected ear. Initially, the ruptures heal, but with disease progression, there are permanent alterations in the morphological features of the membranous labyrinth with loss of cochlear and vestibular neurones. Eventually there is atrophy of the organ of Corti and the vestibular end organ.

Typically, the major loss of hearing occurs in the first few years. In the early stages the hearing loss tends to be reversible, affecting the low frequencies only, but with advancing cochlear involvement, a peaked audiogram can be seen (best threshold at 2000 Hz) and eventually a flat loss is found in a majority of patients. The hearing loss is typically recruiting as identified by stapedius reflex thresholds within 60 dBHL of the pure tone audiometric thresholds at the same frequencies. In general, the longer the patients are followed, the greater the percentage of those who develop bilateral disease. A total of 15% have bilateral disease by 2 years, and by 20 years 30–60% are bilateral. At autopsy, 30% of the temporal bones in patients with Ménière's disease have bilateral involvement.

The early attacks of vertigo are severe, often associated with vomiting. These prostrate the patient for between 2 and 24 h. About 6% of patients develop drop attacks (Tumarkin's crises) and occasionally there is a loss of consciousness from secondary syncope. The differential diagnosis of the attacks of vertigo can be difficult and includes basilar migraine, benign recurrent vertigo and other causes of acute vertigo. With disease progression a canal paresis of the affected ear can be seen on caloric testing.

Bilateral vestibular failure

Bilateral vestibular failure (BVF) in adults is a rare clinical entity characterized by unsteadiness, particularly in the dark, and oscillopsia. BVF is defined by the absence of a nystagmic response to both caloric and rotary stimuli.

There are many causes. Some 50% of cases have associated neurological disease, such as a progressive cerebellar syndrome, or other cranial neuropathies. Gentamicin ototoxicity, vasculitis and malignant meningitis are also causes. Some cases follow bacterial meningitis.

Clinical presentation depends on whether BVF is very longstanding or recently acquired; and if acquired whether this has been a sequential process or had a sudden onset simultaneously affecting both ears. When the loss is sequential, there are episodes of vertigo lasting from minutes to days. These preceding symptoms may be entirely absent in patients with sudden bilateral BVF. Oscillopsia is a common feature, particularly when walking or travelling in a car. It is a result of the loss of the vestibulo-ocular reflex, particularly at high frequencies, i.e. 1 Hz associated with physiological head movements. Unsteadiness in the dark or on rough ground is also typical and patients feel most stable when walking in good lighting conditions and on firm ground. When BVF has been present from infancy, e.g. following neonatal meningitis, the absence of peripheral vestibular function is surprisingly well tolerated. There may be some delay in developmental milestones; eventually, young children may learn to ride a bike. Caution is advised for patients with BVF in certain situations, e.g. swimming underwater.

The diagnosis is suspected when the Halmagyi headthrust test is performed. In patients with BVF, gaze shifts with the head (doll's eye movement) and only after the head movement is there a corrective saccade to bring the object of interest back on to the fovea. The diagnosis is confirmed with caloric and rotary chair testing: no nystagmic response is elicited with ice cold water and chair accelerations of $120°/s^2$, respectively.

Vestibular paroxysmia

The very existence of this clinical entity has been questioned but it is supported strongly by the prompt response to treatment with carbamazepine. There is paroxysmal hyperactivity to vestibular stimulation combined with a functional defect between attacks. The neuro-pathophysiology is attributed to neurovascular compression, much in the same way as trigeminal neuralgia; ephaptic transmission has also been proposed as a mechanism. The following features define the syndrome:

- Short intense attacks of rotational or to-and-fro vertigo lasting seconds to minutes;
- Attacks frequently provoked by particular head positions;
- Impaired hearing permanently or during an attack;
- Audio-vestibular deficits on testing; and
- Exclusion of a central cause.

Motion sickness

This common problem is caused by repetitive stimulation of the vestibular system. Motion sickness occurs frequently at sea and in cars (especially in children), but also with less usual forms of travel such as on a camel or an elephant. Motion sickness is now rare during commercial flights, but it is a problem during space travel, and one reason why the airship industry did not flourish.

Nausea, sweating, dizziness, vertigo and profuse vomiting develop over several hours or less, accompanied by an irresistible desire either to stop moving or return to land. Prostration and intense incapacitating malaise frequently follow, seen typically in seasickness. The distress, incapacity and dehydration caused by severe seasickness should not be underestimated.

Early symptoms at sea are sometimes helped by maintaining visual contact with the horizon, eating and avoiding the stuffy atmosphere of a cabin. Alcohol tends to make matters worse. However, the motion of a vessel is less dramatic close to its centre of gravity, and hence many sufferers, once symptoms have become established, are averse to remaining on deck, and prefer to 'go below'.

Prophylactic antihistamines, vestibular sedatives (hyoscine, cyclizine or cinnarizine) and stem ginger are of some value. Recovery and habituation with no further attacks usually take place between several hours and several days. However, some individuals remain especially prone to recurent bouts of seasickness, and prefer to remain on dry land.

The precise pathogenesis and neuronal circuitary of motion sickness remains relatively little studied – but there is no doubt that its origin is within the semicircular canals, when they are subjected to particular combinations of pitch, roll and yaw.

Management of vestibular disorders

Management of vestibular pathology requires a clear understanding of normal physiology, the mechanisms of dysfunction and compensation, together with the autonomic and psychological sequelae of vestibular pathology. This leads to accurate diagnosis in the majority, therapy for systemic disorders with vestibular features, prompt intervention for emergencies and rehabilitation for chronic vestibular symptoms, both peripheral and central.

The treatment of vestibular pathology involves:

- Specific therapy for systemic disorders with vestibular manifestations;
- Specific pharmacological therapies for labyrinthine disorders;
- Vestibular rehabilitation physiotherapy, including canalith repositioning procedures (CRPs);
- Psychological support; and
- Surgical interventions.

A plan should be established for each patient, to include an explanation of the symptoms. These are often bizarre and not easily understood in the context of ear disease, e.g. visual vertigo in a supermarket. The importance of the patient understanding the rationale of the management programme cannot be overemphasized; this ensures compliance.

Concurrent drug regimens should be evaluated during the general medical assessment. This will allow appropriate management of conditions exacerbating or preventing recovery of vestibular symptoms, e.g. hypertension, diabetes, hyperlipidaemia, arthritis or ophthalmological conditions and drug effects. Treatment for specific vestibular disorders, e.g. Ménière's disease and BPPV should be undertaken. Persistent vertiginous symptoms are managed by intensive vestibular rehabilitation physiotherapy. A regular exercise programme compatible with the patient's age and physical abilities should be commenced. Psychological factors will be addressed by psychotherapy or drugs.

Monitoring of recovery following treatment can prove difficult, as there is a marked discrepancy between vestibular symptoms and signs and vestibular test results. Therefore, outcome measures of recovery have been developed including validated questionnaires documenting vestibular symptomatology, disability and handicap, e.g. the Dizziness Handicap Inventory and the Vertigo Symptom Scale. In addition, validated psychological questionnaires such as the Beck Anxiety and Depression Scales and quality of life evaluations such as the Short Form 36, are commonly used. Functional measurements such as the Dynamic Gait Index, the Functional Gait Index and the Timed Get-Up-and-Go Test may also provide valuable evidence of improvement. In addition, objective resolution of positional nystagmus in BPPV may be of value. Posturographic results can demonstrate improving CoG measurements and more appropriate balance strategies as symptomatic recovery occurs in both peripheral and central vestibular pathology. The ultimate aim is to discharge the patient with full integration into occupational and personal activities.

Drug treatment

Recent developments in neurochemistry have begun to clarify the role of neurotransmitters within the vestibular system, but despite these developments, few of the recent advances have led to the development of new antivertiginous drugs. The treatment of vestibular disorders remains primarily empirical, because of the paucity of high quality clinical drug trials and an evidence-based approach. There are four arms to the pharmacological treatment of vertigo:

1. Vestibular suppressant drugs for acute vertigo;
2. Specific treatment of vestibular disorders, e.g. Ménière's disease, migrainous vertigo and central vestibular disorders;
3. Drugs used to treat systemic diseases that cause vertigo;
4. Experimental drugs, e.g. drugs that may accelerate compensation.

Symptomatic treatment of acute vestibular symptoms

Acute unilateral loss of vestibular function gives rise to symptoms of vertigo, nausea, vomiting, sweating, pallor and diarrhoea. Patients find such symptoms alarming and commonly fear a serious neurological condition such as a brain tumour or a stroke. Simple reassurance is highly effective, but should be followed by an explanation of the underlying pathology giving rise to such symptoms, and appropriate treatment with antiemetics such as hyoscine, prochlorperazine, promethazine, cyclizine or metoclopramide. Buccal administration of prochlorperazine is effective, but intramuscular therapy can be administered if oral preparations cannot be tolerated because of vomiting. Hyoscine may be administered transdermally. In general, antiemetic drugs act by blocking the afferent pathways from the chemoreceptor zone in the area postrema, the gastrointestinal tract and the labyrinth to the medullary vomiting centre.

Secondly, vestibular sedative drugs should be administered acutely. However, there is good evidence that such medication should be prescribed for the minimum period as the drugs interfere with vestibular compensation. Such drugs include anticholinergics (hyoscine, scopolamine), antihistamines (promethazine, prochlorperazine, cyclizine and metoclopramide) and the calcium-channel antagonists (cinnarizine, flunarizine). These latter two drugs, together with prochlorperazine, may give rise to extrapyramidal side effects, and their dosage should be carefully titrated against symptomatic response, especially in the elderly. In addition, flunarizine has been associated with depression.

Diazepam has been widely used, particularly in North America, in the management of acute unilateral vestibular deafferentation and has been reported to be effective as a consequence of the reduction of neural activity and inhibition throughout the central nervous system, including the vestibular nerve and nuclei. Benzodiazepines may be of value in the treatment of vertigo, to counter the anxiety commonly associated with acute vestibular crises. Recent work would suggest the value of steroids in promoting recovery of labyrinthine function in the initial phases of an acute vestibular episode.

Specific treatment of vestibular disorders

Ménière's disease is a commonly misdiagnosed vestibular syndrome, and appropriate treatment requires accurate diagnosis. There are few double-blind randomized studies assessing treatment efficacy in this condition, and it is important to recall the 80% placebo response rate. Medical treatment is either symptomatic, or aimed at influencing the presumed underlying pathological process of endolymphatic hydrops, or sometimes at the hypothesized immunological pathogenesis; surgical treatment aims first to decompress the hydrops, e.g. saccus decompression. Other, destructive procedures in intractable cases include intratympanic gentamicin (so-called medical labyrinthectomy), surgical labyrinthectomy or vestibular neurectomy.

No evidence-based standard treatment protocols exist, and general measures may include lifestyle adaptations such as stress reduction, food elimination and even allergy immunotherapy. Medical therapy commonly includes a low-salt diet and diuretics, although to date there is no clinical trial of sufficient quality to confirm the efficacy of diuretic treatment. Bendroflumethiazide is the thiazide diuretic of choice, although chlortalidone has been reported to be beneficial in early uncontrolled studies; both diazide and acetazolamide have also been advocated.

Betahistine is a histamine analogue that has been reported to bring about a reduction of the asymmetric functioning of the vestibular end-organs, improve microvascular circulation in the stria vascularis of the cochlea and inhibit the activity of the vestibular nuclei. A systematic review identified major flaws in the clinical trials of betahistine and Ménière's disease. With these limitations, the review noted that betahistine may bring about a reduction in vertigo and tinnitus, but no specific therapeutic effect could be confirmed.

Steroids have been used in the treatment of Ménière's disease on the assumption that they may ameliorate an autoimmune diathesis, but there are no double-blind controlled trials to prove their efficacy. Treatment may be taken orally, or topical application via tympanostomy tubes into the middle ear, which may achieve better drug penetration with less side effects than systemic administration. The outcome of steroid treatment and methotrexate remains controversial.

In patients with intractable vertigo, but preserved auditory function, the instillation of intratympanic gentamicin was popularized in the 1990s and has become a common treatment particularly in North America. Gentamicin is predominantly vestibulo-toxic, but no standard treatment protocol or dose has been defined. High rates of therapeutic success in the control of vertigo have been reported, but sensorineural hearing loss has been reported in up to 30% of cases. Moreover, recurrence of vertiginous symptoms may develop in up to one-third of treated cases within 24 months. Careful consideration of this form of management is required, in view of the significant percentage of patients who develop bilateral involvement with Ménière's disease.

Hyperbaric oxygen therapy with continuous variations in pressure has been reported to be of benefit, as has treatment with the Meniett device, which delivers intermittent micropressure pulse waves to the inner ear through a tympanostomy tube. In a prospective randomized placebo-controlled multicentre clinical trial, the Meniett device was reported to show significant improvement in terms of frequency and intensity of vertigo, dizziness, aural pressure and tinnitus but further scientific evaluation is required.

Surgical management of Ménière's disease includes prophylactic measures such as endolymphatic sac decompression, for which there is no firm evidence of efficacy and destructive surgical procedures. These latter techniques are primarily reserved for patients with intractable vertigo and profound hearing loss, with clear evidence of the side of lesion giving rise to symptoms. Surgical options include vestibular nerve section and labyrinthectomy. However, such procedures should be undertaken with extreme caution, not only because of the possibility of bilateral pathology in Ménière's disease, but also because of the possible failure of compensation for a total unilateral vestibular loss.

Migraine

The treatment of migrainous vertigo parallels that of migrainous headache (Chapter 11). Dietary measures, lifestyle adaptation and stress reduction techniques are important, together with psychological management and intensive vestibular rehabilitation physiotherapy, for the 25–30% of patients with migrainous vertigo who demonstrate peripheral vestibular dysfunction.

The pharmacological treatment of migraine includes both prophylactic and acute symptomatic management. Prophylactic treatment should be considered in recurrent acute episodes of vertigo in which symptomatic treatment is inadequate. Beta-blockers such as propranolol, calcium-channel blockers such as cinnarazine, serotonin antagonists such as pizotifen, in addition to tricyclic antidepressants such as amitriptyline, have all been shown to be effective in some cases. Symptomatic treatment may include antivertiginous and antiemetic drugs as well as specific treatment for headache. Triptans have been shown to be highly effective in ameliorating both dizziness and headache and may also relieve nausea, vomiting and phonophobia. Sublingual, subcutaneous or rectal zolmitriptan have been recommended as the duration of migrainous vertigo may be too short to warrant treatment with oral triptans. Ergot drugs and acetazolamide have also been reported to be effective in controlling migrainous vertigo.

Episodic ataxia

Episodic ataxia type 2 (Chapter 16) can present with acute vertigo and ataxia, with or without interval symptoms. Both acetazolamide and 4-amino-pyridine have been reported to help.

Central vestibular dysfunction

Central vestibular dysfunction associated with neurological disease is exceedingly difficult to help. It commonly presents with ataxia and disordered oculomotor function, including bi-directional, dysconjugate, rotatory, vertical, periodic, alternating, see-saw or pendular nystagmus. No single treatment is of benefit to all patients, but an understanding of ocular physiology and the neurochemistry of the vestibular system have enabled a rational approach to specific treatments.

Both clonazepam and 3,4-diaminopyridine have been reported to help downbeat nystagmus, while acquired pendular nystagmus may respond to gabapentin. Baclofen has some effect in periodic alternating nystagmus. No specific treatment regimes have been defined; frequently, drugs are used empirically and doses titrated against response and side effects.

For patients with chronic instability and ataxia of central vestibular origin there is some evidence that intensive vestibular rehabilitation physiotherapy and gait retraining strategies may help both stability and confidence.

Treatment of chronic peripheral vertigo

Vestibular rehabilitation physiotherapy

The majority of patients with persistent chronic vestibular symptoms demonstrate uncompensated unilateral peripheral vestibular dysfunction. Less commonly, patients may present with chronic symptoms caused by bilateral vestibular hypofunction, and for both unilateral and bilateral dysfunction, intensive vestibular rehabilitation physiotherapy is the mainstay of treatment. Every effort should be made to ensure optimal sensory input for balance, i.e. correction of visual/ophthalmological disorders such as cataracts, aggressive management of joint/orthopaedic problems, e.g. arthritis, and medical management of fluctuating vestibular conditions such as Ménière's disease or BPPV.

Compensation cannot be effective in the face of inadequate sensory input or fluctuating vestibular activity. Importantly, anti-emetics and/or vestibular sedative drugs should not be used for chronic symptoms – there is evidence that they impair vestibular compensation. Notwithstanding this fact, there is widespread and inappropriate prescription of these drugs for chronic vestibular symptoms both in primary and tertiary care.

CNS plasticity underpins vestibular rehabilitation and symptomatic vestibular compensation. The Cawthorne–Cooksey exercises are systematic exercises aimed at stimulating visual, vestibular and proprioceptive input on a repetitive basis to enhance compensation. They were initially introduced empirically in the 1940s. In the 1970s and 1980s, animal experimentation provided a scientific basis for their value, providing evidence to support the rationale for specific physiotherapy for chronic vestibular symptoms. Subsequently, a range of vestibular rehabilitation programmes has been devised, containing a number of key elements:

- A detailed explanation of the rationale of exercises, and the aim of therapy to ensure patient motivation and compliance;
- A graded approach, with increasing sensory input and speed of task, to expedite compensation;
- Emphasis upon exercises that are functionally relevant and that actually provoke dizziness in individual patients; and
- Repeated short but frequent repetitions of individual exercises to promote habituation.

Many studies have shown the efficacy of these regimes. Recent research has highlighted that customized exercises with a programme devised specifically for each patient, based on individual vestibular limitations, is most effective. Mechanical exercise programmes including optokinetic stimulation, visual flow stimuli and rotational stimuli have been shown to be especially helpful and to optimize vestibular compensation. Other strategies shown to enhance compensation include virtual reality Tai Chi and support surface translations.

Traditionally, vestibular rehabilitation physiotherapy has been used in the treatment of unilateral peripheral vestibular disorders that have failed to compensate. Many factors are associated with failure of compensation (Fig. 14.14) and most can be targeted with physiotherapy, by specific evaluations including standardized health report questionnaires, scored balance assessment tests and dynamic posturography. These measures also document recovery, support patient motivation and cooperation and direct ongoing physiotherapy.

It cannot be overemphasized that a detailed explanation of the underlying pathological processes, with a basic understanding of vestibular compensation, is crucial if the patient is to accept that physiotherapy rather than some alternative, technically sophisticated option is more appropriate. Early intervention may be beneficial, but neither long-standing symptoms nor old age are negative prognostic factors – enthusiastic treatment is always worth trying.

Recent work has also confirmed the value of vestibular rehabilitation physiotherapy in the management of migraine, bilateral vestibular failure and central vestibular pathologies including brainstem and cerebellar disease. An important group of patients, whose symptoms are frequently found to be intractable to standard rehabilitation techniques, are those with visual dependence and visual vertigo. In this group, optokinetic training and mechanical rehabilitative interventions have been shown to be of value. Virtual reality stimulation may be of specific value in this group. A further subset of patients with persistent dizziness are those with vestibular pathology associated with psychological symptoms. This group undoubtedly benefit from vestibular rehabilitation physiotherapy, although a range of psychological support measures should be provided in parallel.

Particle repositioning procedures

BPPV is the most common vestibular syndrome and requires specific particle repositioning procedures aimed at addressing the underlying mechanism of cupulo- or canalithiasis. Accurate diagnosis is crucial for three reasons:

1 Central positional nystagmus, although rare, may indicate serious life-threatening neurological pathology;
2 Management of cupulolithiasis and/or canalithiasis of each of the three semicircular canals requires specific different interventions;
3 The correct specific particle-repositioning procedure is highly successful for these debilitating conditions.

The symptoms associated with BPPV commonly abate over several weeks, but in some 30% symptoms persist, with significant disability and distress. Many different procedures for BPPV have been described, but the three established techniques are the Brandt–Daroff exercises, the Semont liberatory manoeuvre and the Epley particle-repositioning procedure.

The Brandt–Daroff exercises were devised for the treatment of cupulolithiasis, and consist of rapid movements of the body and head from one lateral position to the other (Fig. 14.17).

The technique is particularly valuable in patients who have been unresponsive to the single particle repositioning procedures, or in patients who are unable to seek professional advice, e.g. those who travel extensively with their work, or live at a distance from prompt medical help. In the 1980s, Brandt and Daroff reported relief from BPPV within 14 days in their patient group, although a controlled study revealed resolution in only 23% of patients after 1 week.

The Semont manoeuvre, developed to liberate otolithic deposits from the cupula of the posterior semicircular canal, is conducted by lying the patient on the affected side with the face turned 45° towards the ceiling.

The patient is then rapidly swung in an arc through the sitting position, to lie on the opposite side with the face turned downwards by 45°. This latter position should be maintained for 5 min prior to the patient being brought slowly up to the sitting position (Fig. 14.18).

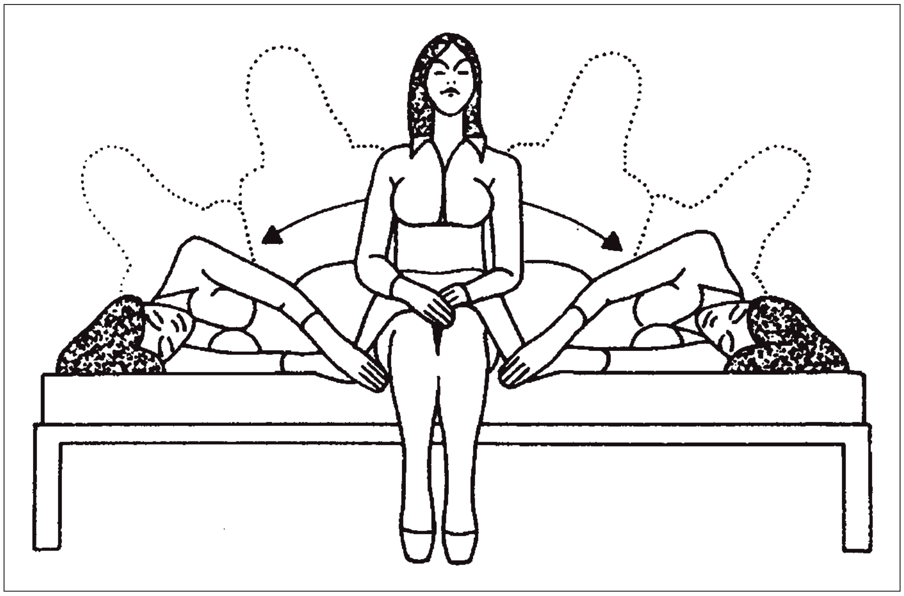

Figure 14.17 Brandt–Daroff exercises. (From Brandt & Daroff 1980, reproduced with permission.)

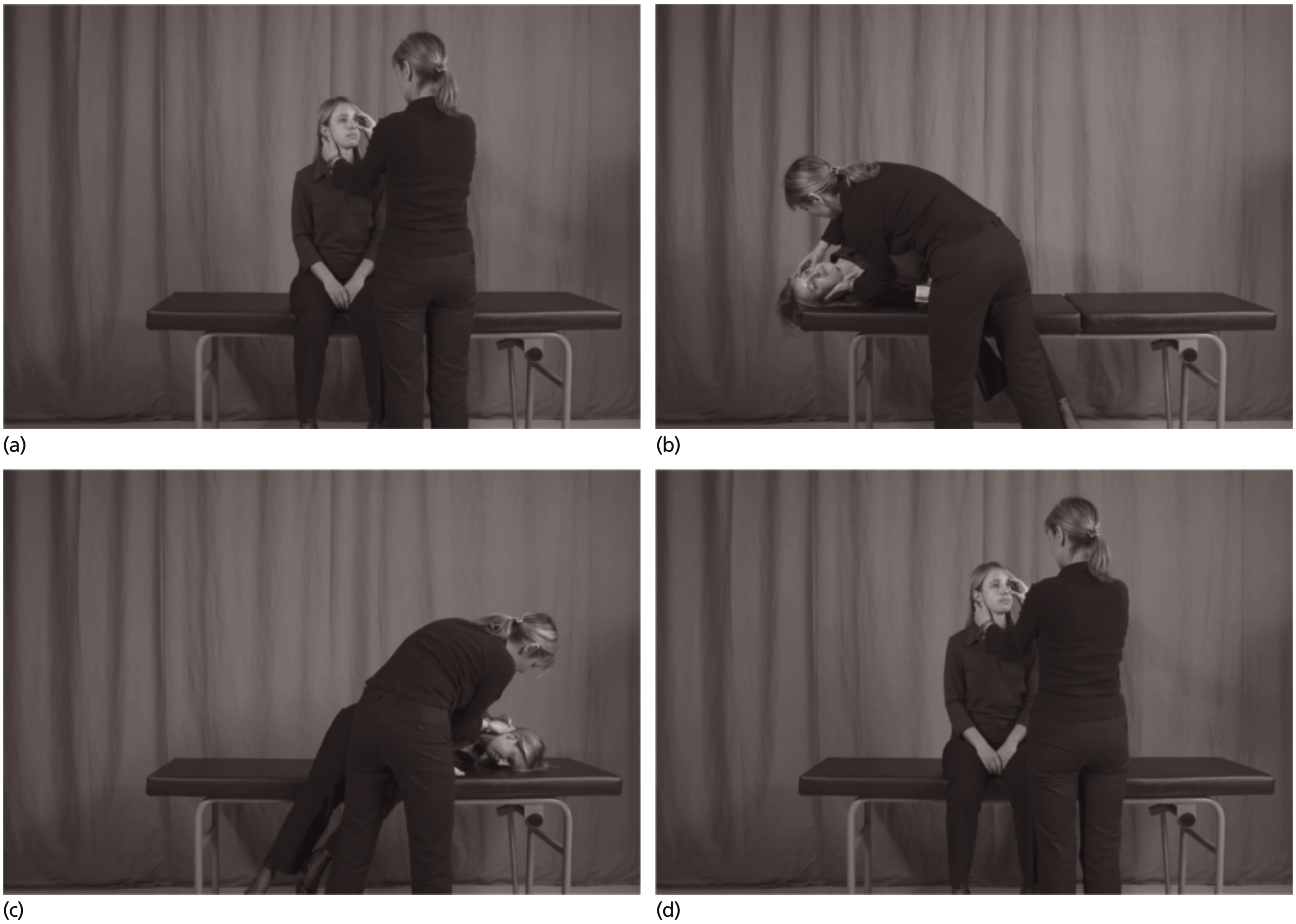
(a) (b) (c) (d)

Figure 14.18 Semont manoeuvre. (From Luxon 2006, with permission.)

The Epley particle repositioning procedure (1992) was introduced as a successful technique for treating p-BPPV (Fig. 14.19). Subsequently, the technique has been adapted for the treatment of a-BPPV and h-BPPV.

The manoeuvre is comprised of five separate positions, the first being the Dix–Hallpike manoeuvre for the identification of p-BPPV. The various positions that are then assumed result in the otoconial debris moving to the most dependent part of the posterior canal, and from there to the common crus and then out of the canal into the vestibule where, upon assuming the critical head position, debris does not fall on to the cupula of the posterior canal.

Both the Epley and Semont manoeuvres have been widely evaluated, for both subjective outcome and objective absence of positional nystagmus. They are highly effective, with around 90% of patients becoming symptom-free after repeated manoeuvres. Some evidence suggests the best recovery rate is in cases where vertigo has been caused by vestibular neuritis, while those cases caused by trauma have a poorer outcome, with a recurrence rate of some 50% at 5 years. Importantly, it is well recognized that p-BPPV can convert to a-BPPV after a particle repositioning procedure; careful observation of nystagmus is required to ensure that an appropriate second procedure is conducted where the first appears to have failed.

Specific treatments for h-BPPV and a-BPPV have been described. Horizontal dysfunction may be treated with a 12-h prolonged positioning on the healthy side (Vannuchi manoeuvre), while an adapted Epley manoeuvre and 270° rotation around the longitudinal axis (Lempert roll manoeuvre) have both been reported to be effective. a-BPPV can be treated with a reverse repositioning procedure, i.e. a right a-BPPV can be treated with a left canal repositioning procedure.

Physical treatments for BPPV are highly effective, and <1% require surgical intervention. Historically, vestibular nerve section has been carried out, but the surgical treatment of choice in intractable cases is now considered to be occlusion of the posterior semicircular canal.

Psychological treatment

Psychological symptoms in association with vestibular pathology are well recognized and frequently result in intense and protracted symptoms when there has been failure to compensate from a vestibular deficit. Many studies have highlighted the

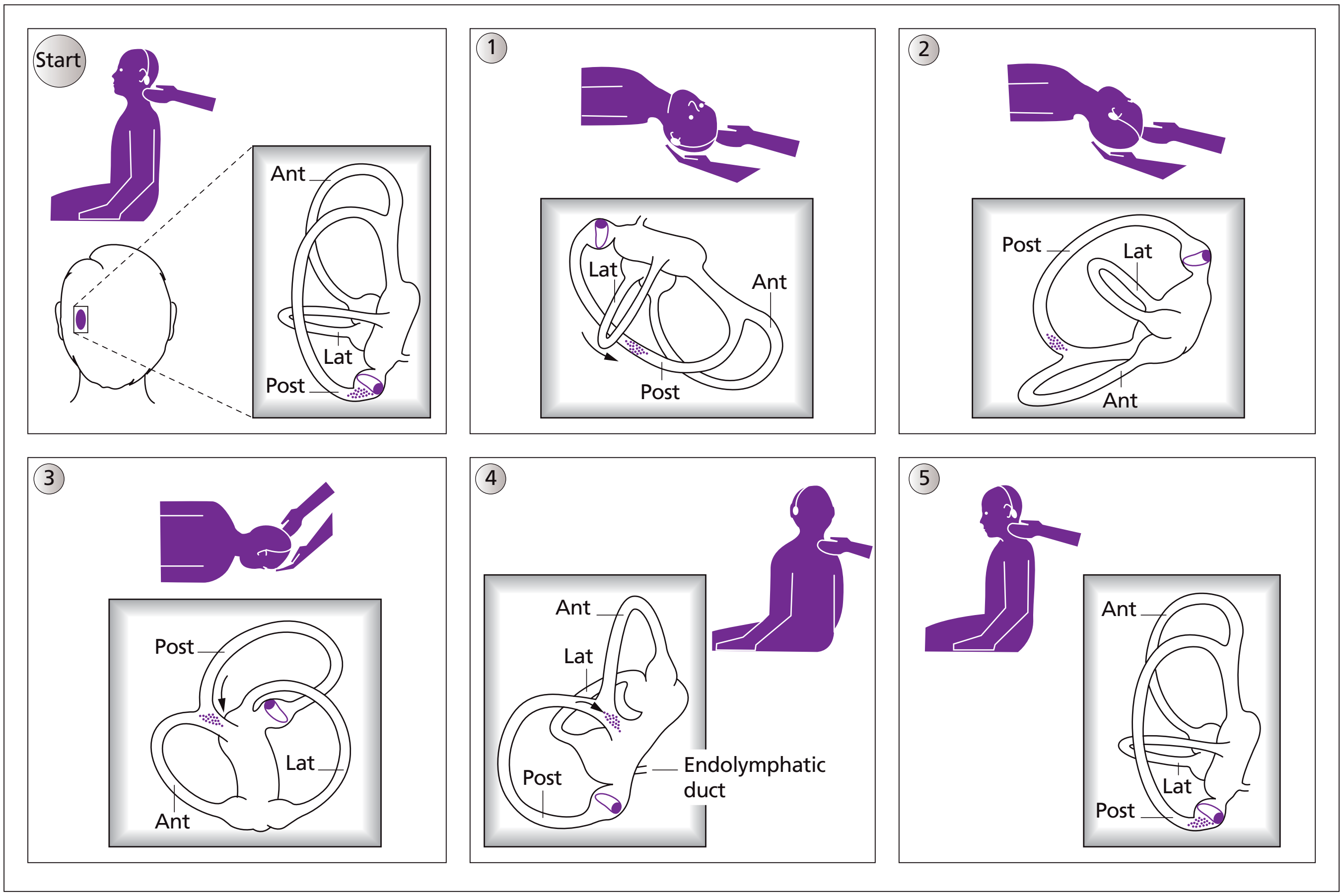

Figure 14.19 Epley manoeuvre. (From Epley 1992, with permission.)

association of agoraphobia, anxiety states, panic attacks, depression and avoidance behaviour, together with phobias such as space and motion phobia in patients with vestibular symptoms. Recent work has outlined a possible underlying neurological basis for the relationship between anxiety and vestibular symptoms. Psychological support is a key factor in rehabilitation of many patients with vestibular symptoms and should always be considered when there is no satisfactory explanation either for failure to recover, or decompensation following earlier improvement.

Importantly, the clinician should understand the interaction of psychological and vestibular factors, in order to provide a satisfactory and understandable explanation of the way in which the patient's symptoms are compounded by the interaction of these two aspects of the illness. The specific mode of treatment will depend on the primary underlying psychological disorder: avoidance behaviour, panic attacks, phobias, anxiety states and/or depression. Cognitive–behavioural therapy in parallel with physiotherapy is invaluable in patients who have developed avoidance behaviour and/or panic attacks, while formal psychiatric intervention is required in patients with anxiety states and depression. The index of suspicion of an underlying psychological problem should be high in patients with vestibular dysfunction.

Surgical management of vertigo

Surgical intervention for the treatment of isolated vertigo is rarely needed. The major conditions requiring surgical intervention are life-threatening complications of otitis media, cerebellopontine angle tumours and perilymph fistulae. Surgical procedures may be divided into those aimed at alleviating underlying pathophysiology, e.g. canal-plugging procedures in BPPV and endolymphatic sac decompression for Ménière's disease, although there is little evidence to support the latter intervention. Intractable vertigo with good hearing in Ménière's may be treated by destructive procedures such as vestibular neurectomy or chemical labyrinthectomy (gentamicin) while intractable vertigo with profound hearing loss may be treated with surgical labyrinthectomy. It should be reiterated that destructive procedures should be undertaken with great caution, for two reasons:

1 The possibility of the development of bilateral vestibular dysfunction, e.g. in the case of Ménière's disease or head trauma; and

2 The possibility of persistent vertigo from poor vestibular compensation: there is scant evidence to suggest that total vestibular loss will compensate more effectively than partial vestibular failure.

In conclusion, simple treatment strategies are highly effective for the majority with these distressing and incapacitating symptoms. This is particularly important for the neurologist, who is frequently referred a patient whose symptoms have defied diagnosis and management by an otological colleague. A rational approach to the diagnosis and management of vestibular symptoms is cost-effective for the health care system and has significant personal and occupational benefits for the patient.

Hearing disorders: introduction

Disorders of the ear represent 24% of all disabilities in the adult UK population – a major cause of morbidity. Hearing loss is the most common sensory disability worldwide, with an estimated 278 million people suffering moderate to profound impairment in both ears. Hearing loss can follow pathology in the external, middle or internal ear and in retro-cochlear and central auditory pathways. It is judged by the threshold of hearing across a standard frequency range of 250–8000 Hz. For clinical purposes, threshold values better than 20 dBHL are considered to be normal.

In children, in the UK, 1.1/1000 babies are born with permanent bilateral hearing impairment; this figure doubles by the age of 16. Twenty-five per cent of children below 4 years of age have otitis media with effusion and associated hearing loss; perhaps 10% of children are estimated to have some degree of auditory processing disorder. Of the UK population over 50 years, 35% have at least mild loss of hearing.

Hearing impairment and deafness have profound socioeconomic and psychological consequences. Without appropriate care, children may fail to develop normal speech, language and cognitive skills which limit educational and occupational choices. Adults are less likely to be in skilled employment, find it difficult to progress in their occupational environment and suffer social stigmatization, isolation and a high incidence of psychiatric illness.

Tinnitus is a perception of a sound that originates from within the body rather than the external world. It affects about 10% of most populations studied; about half find tinnitus sufficiently intrusive to seek help. If perceived solely by the patient tinnitus is called subjective, while objective tinnitus refers to sound audible externally – it has a physical source, such as palatal myoclonus, an arterio-venous fistula or turbulent flow through a stenotic artery. Occasional tinnitus is an almost universal perception, but the prevalence of persistent tinnitus is positively correlated with age and female gender. Tinnitus increases with progressive hearing loss, of all aetiologies. However, tinnitus as a complaint and its degree of intrusiveness has strong correlations with psychological factors rather than demonstrable physical features.

Hyperacusis is the most common dysacusis, occurring in some 6–7% of the population. Hyperacusis means a reduced tolerance to noise or an increased sensitivity to sounds at levels that would not cause discomfort in a normal individual. In the majority it is associated with normal hearing, but it is reported in 40–80% of people with tinnitus. Hyperacusis differs from loudness recruitment, which refers to oversensitivity to loud sounds.

Auditory neuropathy, first described in 1996, describes patients in whom hearing impairment is characterized by disordered processing of sound (see below). Generally, these disorders are retrocochlear; however, the notion of a peripheral auditory lesion impacting on auditory synchrony is an emerging concept. Cases are not uncommon – some 5–12% of those previously considered to have severe hearing disorder in paediatric populations, and are a heterogeneous group. The importance of recognizing these patients is well established: they have specific management requirements.

Impaired structure and/or function of the auditory brain may have little or no effect on hearing thresholds, but may cause deficits in other aspects of hearing; these deficits are referred to collectively as auditory processing disorders (APD). In 1954, Bocca and colleagues first observed that patients with temporal lobe tumours have hearing difficulties, despite normal audiograms, and found deficits on a speech test in which frequency components of the speech signal had been removed. APD is now recognized as a distinct entity. However, diagnosis remains a challenge, not only because of the complexity of the auditory brain, but also because of the lack of accepted diagnostic criteria, and any systematic diagnostic test battery.

Hearing disorders: basic concepts

Hearing loss and tinnitus most commonly indicate cochlear dysfunction, but may reflect either VIIIth nerve or central auditory pathology with normal cochlear function. These latter pathologies characteristically present with difficulties hearing in conditions of poor signal : noise ratio, e.g. in the presence of background noise, and sound localization. Hearing loss and/or tinnitus, with or without associated vestibular abnormalities, is most commonly caused by otological pathology. However, cochlear, VIIIth nerve or central auditory dysfunction may be part of the presentation of a neurological disorder. To understand these sources of disordered hearing, the following section outlines basic concepts associated with each site of dysfunction.

Conductive hearing loss

Pathology affecting the external and middle ear causes abnormalities of mechanical transmission of sound waves from the environment to the cochlea, known as conductive hearing loss. Typically, the amplification afforded by middle ear enhancement of the auditory signal is 10^6, and pure conductive hearing losses do not exceed 60 dBHL across the speech frequencies detected by the pure-tone audiogram.

Sensorineural hearing loss

Pathology of the cochlea and VIIIth nerve gives rise to sensorineural hearing loss in which there is an inability to transduce the

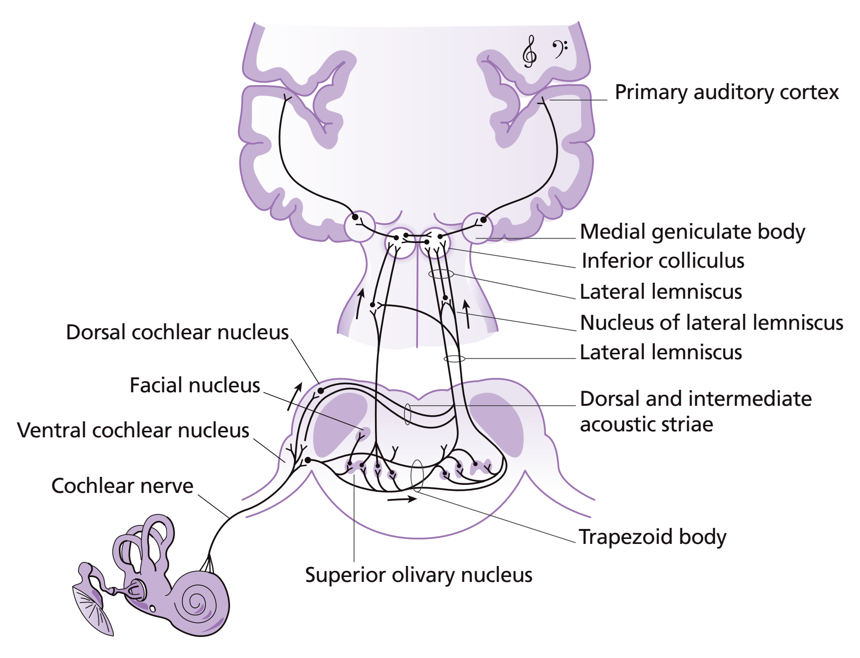

Figure 14.20 Afferent auditory pathway. (From Noback 1981, with permission.)

mechanical energy of sound waves into electrical activity within the cochlea or transmit the signals along the VIIIth nerve (Fig. 14.20).

There is, in addition, an inability to perceive both bone and air conducted sounds, and both the intensity of sound and the frequency resolution of complex sounds are impaired. Sensorineural hearing loss may be further divided into that of cochlear origin and that of neural origin on the basis of two pathophysiological phenomena:

1 *Loudness recruitment*: this is an abnormally rapid increase in loudness with an increase of intensity of stimulus. Loudness recruitment is characteristic of disorders affecting hair cells of the organ of Corti, but is absent in VIIIth nerve and brainstem pathology.
2 *Abnormal auditory adaptation*: this is a decline in discharge frequency with time, observed following an initial burst of neural activity in response to an adequate continuing stimulus applied to the organ of Corti. This phenomenon is characteristic of neural auditory dysfunction arising in both VIIIth nerve and the brainstem.

Auditory neuropathy

The term auditory neuropathy has arisen as a way of grouping together, on a functional basis, those hearing disorders where there is impairment of the temporal synchrony of sound. Characteristically, a particular constellation of observations of inconsistent measures of hearing are found: speech thresholds are markedly impaired, pure tone audiometric thresholds are relatively well preserved and acoustic brainstem evoked responses (ABR) are found to be delayed or absent. Thus, loudness of sound is relatively well perceived, but synchronization of acoustic signals is not adequate to evoke an ABR. This lack of synchronization can also affect the stapedius reflex, and the suppression of contralateral otoacoustic emissions. Because this synchronization requires integrity of the VIIIth nerve, these cases of hearing loss have been described as 'auditory neuropathy/dys-synchrony (AN/AD)' or auditory neuropathy spectrum disorder.

It is generally agreed that the term auditory neuropathy encompasses heterogeneous conditions where the lesion may occur anywhere along the auditory pathways, from the inner hair cells of the cochlea distally, through to the auditory brainstem pathways centrally. With further assessment of these patients over the last two decades, a more accurate umbrella term overarching these disorders may be 'neural synchrony disorders'. There is evidence accumulating to implicate at least three different sites of lesion:

1 Electromechanical transduction at the inner hair cells (including synaptic transmission);
2 Axons, cell bodies and myelin sheaths;
3 Efferent influences through the olivo-cochlear feedback pathways.

The concept of auditory neuropathy has challenged thinking about the physiology of hearing, and has provided a model for examining the role of neural synchrony of the VIIIth nerve and brainstem, and its impact on auditory perception.

Brainstem auditory dysfunction

The auditory nuclei in the brainstem are important for auditory processing for two reasons: extraction of signals from a background of noise that has led to the development of auditory separation tasks; and binaural integration of auditory information that has led to the development of binaural interaction tasks. Behavioural tests of particular value in assessment of brainstem disorders include: masked speech, the synthetic sentence identification with ipsilateral computing message test, the masking level difference test and the binaural fusion test.

Auditory processing disorders

The British Society of Audiology (BSA) recently proposed that APD 'results from impaired neural function and is characterized by poor recognition, discrimination, separation, grouping, localization, or ordering of non-speech sounds. APD does not result solely from a deficit in general attention, language or other cognitive processes.' Similarly, the American Speech-Language-Hearing Association (ASHA, 2005) proposed that the term 'central' should precede the term APD, because 'most definitions of the disorder focus on the central auditory nervous system' and thus defined (C)APD as 'a deficit in neural processing of auditory stimuli that is not due to higher order language, cognitive, or related factors'. Patients with APD may show deficits in sound localization, auditory pattern recognition, and sound discrimination, temporal processing, processing of degraded auditory signals or processing of the auditory signal when embedded in competing acoustic signals. However, APD is not yet included in current classification schemes of developmental/higher order disorders, and this term should perhaps be interpreted to mean 'disordered auditory processing' rather than 'auditory processing disorder'.

Anatomy and physiology

Anatomically, the ear is divided into the external, the middle and the internal ears (Chapter 2). Physiologically, the external and middle ears collect, enhance and amplify sound. Acoustic information is transmitted through the middle ear to the cochlea where the inner hair cells of the organ of Corti transduce mechanical energy into electrical activity, which is conveyed to type 1 auditory afferent fibres. The outer hair cells of the organ of Corti are thought to act as both modulator and amplifier, capable of fine tuning receptor function of the cochlea. Auditory signals from the organ of Corti are transmitted along the afferent auditory pathway (Fig. 14.20): auditory nerve → ipsilateral cochlear nucleus. Thence, the majority of afferent auditory fibres project to the contralateral superior olivary complex, lateral lemniscus, inferior colliculus, medial geniculate body and onwards to the auditory cortex.

The auditory efferent pathway (Fig. 14.21) arises in the auditory cortex and descends in parallel to the afferent pathway. The anatomy of the higher efferent auditory system remains ill-defined, but within the brainstem the olivo-cochlear bundle projects from the superior olivary complex to the cochlea via two main pathways:

1 Medial olivo-cochlear system that projects mainly to the contralateral cochlea and connects to the outer hair cells of the organ of Corti; and

2 Lateral olivo-cochlear system that projects to the ipsilateral cochlea and ends on the type 1 afferent dendrites that connect to the inner hair cells of the organ of Corti.

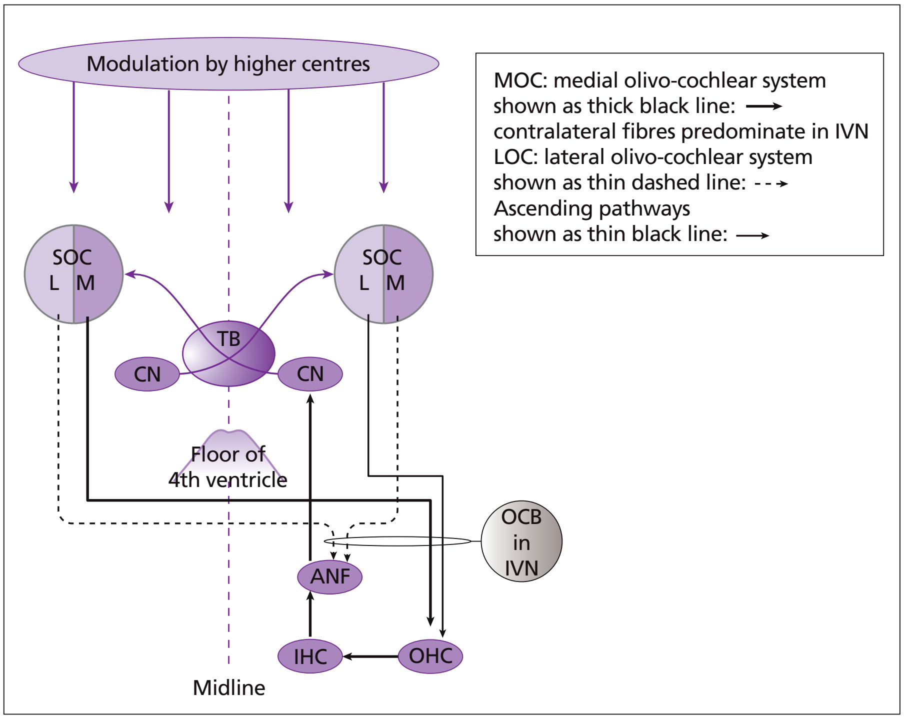
Modulation by higher centres
MOC: medial olivo-cochlear system
shown as thick black line: ⟶
contralateral fibres predominate in IVN
LOC: lateral olivo-cochlear system
shown as thin dashed line: - - →
Ascending pathways
shown as thin black line: ⟶
SOC
L M
SOC
L M
TB
CN
CN
Floor of
4th ventricle
OCB
in
IVN
ANF
IHC
OHC
Midline

Figure 14.21 Efferent auditory system. Ascending pathways shown as double lines; ANF, auditory nerve fibre; CN, cochlear nucleus; IHC, inner hair cell; IVN, inferior vestibular nerve; LOC, lateral olivo-cochlear system shown as thin dashed line, ipsilateral fibres predominate in IVN; MOC, medial olivo-cochlear system shown as thick black line, contralateral fibres predominate in IVN; OCB, olivo-cochlear bundle; OHC, outer hair cell; SOC, superior olivary complex; TB, trapezoid body. (From Murdin 2008/Ceranic 1998, with permission.)

Efferent fibres leave the brainstem in the inferior division of the vestibular nerve. The precise functions of the efferent auditory system remain poorly understood, but amongst the suggested hypotheses are that it shifts the dynamic range of hearing to enhance signal detection and frequency selectivity; that it protects the ear from excessive noise and that it aids selective attention.

Clinical examination of the ear and hearing

Examination of the auricle, the external auditory meatus (EAM) and the middle ear, in as far as they can be assessed by examination of the tympanic membrane (TM), is directed towards identifying any otological pathology that points to a peripheral rather than a central neuro-otological lesion. The tympanum offers a window into the middle ear cleft and is affected by most changes that can take place within the middle ear. Otitis externa, acute otitis media or TM perforation contraindicate caloric testing, a cornerstone of vestibular investigation. Wax in the aural cavity also precludes caloric irrigations because it acts as a heat seal and, when impacted, gives rise to spurious conductive hearing loss.

Otoscopy

Inspection of the ear is carried out with an otoscope or using a head-worn light source, leaving the hands free. Directing the speculum around the circumference of the outer ear canal allows debris, foreign bodies, inflammation and defects of the posterior or anterior wall to be identified. The Siegel (pneumatic) speculum can be fitted and the bulb squeezed to vary intra-meatal pressure. In the presence of a middle ear effusion, the TM is immobile. However, with a flaccid TM, this may have been sucked back on to the middle ear mucosa; lowering the pressure may suck it out again, allowing a retraction pocket to be distinguished from a perforation.

Auricle (pinna)

Any congenital abnormality of the auricle will be fairly obvious, but must be identified because of the likely associated findings of middle and inner ear abnormalities, e.g. anotia (absent auricle) or microtia (smaller than normal and often misshapen auricle). Pre-auricular appendages are found in 1.5% of the population; fistula auris, a small blind pit seen anterior to the tragus, results from incomplete fusion of the auricular tubercles.

External auditory meatus

Congenital conditions include a stenosed or atretic EAM. In the latter, the EAM is closed over with a membranous straight bony wall across the canal. Acquired abnormalities include foreign body obstruction; otitis externa – caused by *Staphylococcus*, *Pseudomonas* and diphtheroids, fungal infections such *Aspergillus* and *Candida*, and viral infections such as zoster (Ramsay-Hunt syndrome). Osteomas are rounded excrescences of bone; exostoses are small osteomas, common in those who swim or dive frequently.

Tympanic membrane and middle ear

Wax, if impacted or obscuring the TM, can be removed with a head-light using the Jobson horn probe, or a Cawthorne wax hook or by syringing. If the wax is very hard, it can be softened over a period of weeks using warm olive oil drops administered nightly, or alternatively 5% sodium bicarbonate drops, or other wax dissolvers (ceruminolytics).

The standard TM landmarks are:

- The central portion with handle of the malleus, visible through the drum;
- The pars flaccida superiorly, and the pars tensa inferiorly;
- The long process of the incus; and
- The stapedius tendon.

The following abnormalities are important to identify.

Perforations

These are divided into marginal (unsafe) or central (safe) perforations in the pars tensa, and attic perforations.

Colour and position of the membrane

The normal eardrum has the appearance of mother-of-pearl. The light reflex, seen antero-inferiorly, may be lost if the membrane is thickened. White patches of tympanosclerosis are a result of hyaline degeneration, when the middle layer of fibrous tissue is impregnated with deposits of calcium. Blood may be seen behind the TM, and manifestations of infection visible.

Retraction of the membrane occurs when there is chronic lowering of pressure within the middle ear, i.e. with chronic obstruction of the Eustachian tube. When severe, the drum is stretched around the long process of the incus and head of stapes, and at worst, the membrane is plastered against the promontory. A fluid level may be visible if secretory otitis media has resulted from reduction of middle ear pressure. Air bubbles confirm middle ear fluid. A bulging drum may occur with raised middle ear pressure (normal colour) or with acute suppurative otitis media (cherry red).

Fistula sign

This is seen in patients where air pressure changes in the EAM are transmitted into the labyrinth, via a fistula (Table 14.11).

Table 14.11 Fistula sign.

This comprises the following:

- Raised pressure causes a conjugate deviation of the eyes towards the opposite ear
- With maintenance of pressure, a corrective fast eye movement (nystagmus) will be introduced towards the affected ear

Depending on where the fistula has developed, the nystagmus will be:

- Horizontal (horizontal semicircular canal)
- Torsional (anterior canal)
- Vertical (posterior canal)

External auditory meatus pressure can be raised by pressure on the tragus, but more accurately by tympanometry. Hennebert's sign is a positive fistula sign in the presence of an intact tympanic membrane

Table 14.12 Rinne tuning fork test.

Heinrich Rinne described his tuning fork test in 1855:

1. The fork is struck and held with the tines perpendicular to the long axis of the external auditory meatus with the closest tine 1 cm from the entrance to the meatus
2. The patient is asked to report if they can hear the sound (AC)
3. The fork is immediately transferred behind the ear with the base firmly pressed to the bone overlying the mastoid (BC)
4. The patient is asked which sound is louder: that in front of the ear, or that behind the ear?

The Rinne test is positive if AC > BC, i.e. the sound in front of the ear is reported as the louder. This indicates:
- Normal hearing, or
- An ear with a sensorineural hearing loss

The Rinne test is negative if BC > AC, i.e. the sound in front of the ear is reported as the quieter. This identifies:
- A significant conductive component of hearing loss of >15 db
- *But*, a false negative Rinne test can occur if there is severe sensorineural hearing loss in the tested ear; the BC stimulus is heard in the non-tested ear because of transcranial transmission, and thus will be louder than AC sound. This can be overcome by masking the non-affected ear with a Barany noise box

The Rinne test has a high specificity for conductive hearing loss, but a low sensitivity, this not reaching 90% until the air–bone gap >30 db

Table 14.13 Weber tuning fork test.

Weber tuning fork test

The aim of Ernst Weber's test (1934) is to identify the better hearing cochlea. It is used in conjunction with the Rinne test and is of most use in patients with unilateral hearing loss:

1. The 512-Hz tuning fork is struck and placed to the head in the midline, either at the vertex or on the forehead
2. The patient is asked to say whether the sound is heard better in one ear, or equally in both ears

A central Weber is described if the tone is heard centrally:
- This identifies a patient with normal hearing

A lateralizing Weber is when the tone is heard to one side:
- This identifies the side of the better hearing cochlea
- *But*, if there is a conductive component to the hearing loss, the tone may be heard in the poorer-hearing ear (Table 14.12)

Results need interpretation with care and only in conjunction with further hearing tests

Tuning fork tests

Tuning fork tests (Tables 14.12 & Table 14.13; Chapter 3) were used traditionally to distinguish conductive from sensorineural hearing loss, and also to identify functional hearing loss. With pure-tone audiometry, these tests are less used clinically. The principles of tuning fork tests are:
- The inner ear is more sensitive to sound conducted by air than bone;
- In pure conductive hearing loss, the affected ear is subject to less environmental noise and is more sensitive to bone-conducted sound.

The most commonly used tuning forks are those at 256 and 512 Hz. Lower frequencies produce a vibro-tactile stimulus that result in misleading thresholds. A 256 Hz tuning fork distinguishes air–bone gaps better than a 512 Hz fork. The prong (tine) should be struck against a firm but elastic mass, e.g. a rubber pad, two-thirds along the tines, to prevent production of overtones and minimize distortion products.

Audiological investigations

The clinical findings point to the appropriate test battery to investigate hearing loss in detail. The cornerstone of audiological testing is the pure-tone audiogram (PTA), a screening test that measures hearing thresholds. The PTA demonstrates the existence of and extent of hearing loss and determines whether the loss is conductive or sensorineural, or both. The test requires cooperation and is thus a subjective estimate of hearing thresholds. As a psycho-acoustic measurement, audiometry results may be biased by the methods of conducting the test; a well-defined procedure must be adopted. If the patient is unable or unwilling to cooperate, additional audiological investigation is essential to provide objective measures of hearing. Additional tests include measurement of oto-acoustic emissions; stapedius reflex threshold measurement and auditory evoked responses recorded at brainstem, midbrain and cortical levels. Tympanometry is the objective determination of middle ear pressure; the purpose of this aural admittance test is measurement of static acoustic impedance and characterization of tympanometric shape.

Auditory tests aim to define pathology within the auditory system, and to site the level of the lesion. A battery of audiological tests is required to:
- Quantify the audiometric threshold at each frequency;
- Differentiate conductive from sensorineural hearing loss;
- Differentiate cochlear from retro-cochlear abnormality;
- Identify central auditory dysfunction in the brainstem, midbrain or auditory cortex; and
- Identify any non-organic hearing impairment.

Baseline audiometric tests

Pure-tone audiometry

This is the most widely available subjective quantitative test of auditory threshold. The technique, performed in a sound-proofed room with standardized protocols allows the severity, symmetry and configuration of hearing loss to be defined across frequencies 125–8000 Hz in each ear. Electrically generated pure tones are delivered by headphones, and the subject is required to respond to the quietest tone, this being recorded as the hearing threshold for that frequency. Sound is delivered either via air conduction or via bone conduction, using a bone vibrator on the mastoid process. For bone conduction, because the intra-aural attenuation for bone conducted sound is negligible, the ear not being tested is masked with narrow-band noise centred on the test frequency. Bone conduction thresholds significantly better than air conduction thresholds indicate a disorder affecting transmission of sound through the middle ear into the inner ear, i.e. conductive hearing loss, whereas bone conduction and air conduction thresholds that are similar imply sensorineural hearing loss.

Acoustic impedance measurements

Tympanometric measurements provide information about pressure within the middle ear and TM compliance. Passive measurements are made of the change in acoustic impedance or immittance of the TM as a function of the pressure in the sealed external acoustic meatus. High impedance abnormalities include a perforated TM, middle ear effusion, retracted TM or ossicular fixation. Low impedance abnormalities include thin atrophic TMs and ossicular disruption following head trauma.

Stapedius reflex measurements provide information about the inner ear, in addition to the VIIIth nerve and brainstem function. Dynamic changes are measured, resulting from contraction of stapedius, and stapedius reflex thresholds, in response to stimuli of 500, 1000, 2000 and 4000 Hz, at intensities of 70–100 dB sound pressure level. These provide evidence of recruitment and abnormal auditory adaptation, and allow an assessment of middle ear, cochlear, VIIIth nerve and brainstem auditory function.

Speech audiometry

Speech audiometry is concerned with assessment of auditory discrimination as opposed to auditory acuity. The test is subjective and requires the subject to repeat standard word lists delivered through headphones at varying intensities. The responses are scored to provide an assessment of auditory discrimination which, together with other tests, is valuable in distinguishing conductive and sensorineural hearing impairment. This is of particular value in assessing efficacy of hearing aids.

Speech recognition tests are also an essential item of the test battery for identification of auditory neuropathy. Speech intelligibility scores, tested at comfortable hearing level, are reduced disproportionately to the extent of the pure-tone impairment. These scores are calculated from the average audiogram thresholds at 1, 2 and 4 kHz, and if the score falls below predicted values, the hearing impairment is likely to be retro-cochlear in nature.

Electro-acoustic and electrophysiological tests

Event-related potentials provide the most objective technique of assessing auditory function and the functional integrity of their generators, and help to site pathology within the auditory system:

- 'Early', i.e. oto-acoustic emissions (OAE);
- Electro-cochleography (ECochG);
- Acoustic brainstem evoked responses (ABR);
- 'Middle', i.e. middle latency responses; and
- 'Late', i.e. cortical evoked responses.

Oto-acoustic emissions

OAE, first characterized in 1978, are low-intensity sounds generated by the contractile elements of the outer hair cells in the cochlea in response to acoustic stimuli (Fig. 14.22). These

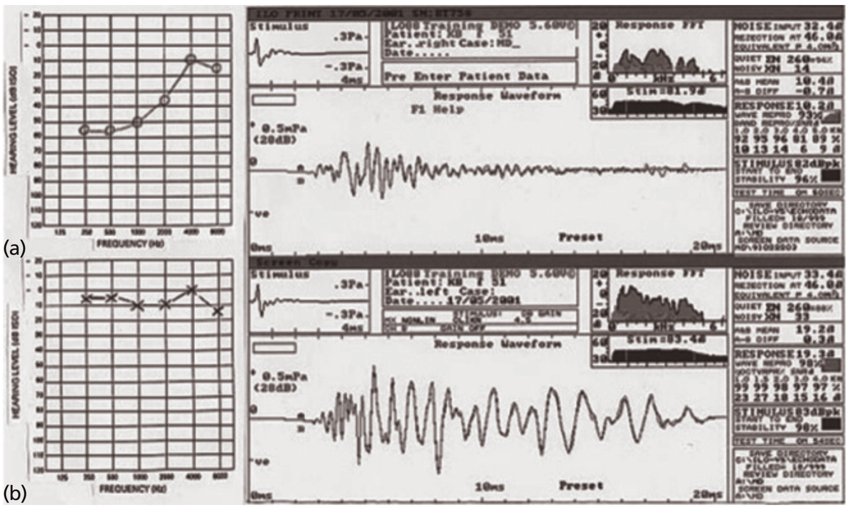

Figure 14.22 Oto-acoustic emissions in patient with Ménière's disease. (a) Right ear of patient: pure-tone audiogram (PTA) showing typical low frequency hearing loss; transient evoked oto-acoustic emissions (TEOAE) showing reduced response. (b) Left ear of patient: PTA showing normal hearing; TEOAE showing normal response. (From Ceranic with permission.)

responses are measured in the external auditory canal, and are a marker of cochlear function. They are left intact after section of the auditory nerve. These acoustic echoes are evoked by stimulation with transients (clicks) at 80–86 dB sound pressure and are known as transient evoked OAE (TEOAE). Typically, responses to 260 stimuli are captured over a time frame of 20 ms after stimulus application. Contralateral suppression of TEOAE occurs if noise (set at a level 5 dB louder than the click) presented to the contralateral ear, reduces the TEOAE by 1 dB or more. Efferent auditory function can be assessed by oto-acoustic emission suppression brought about by the application of noise to the contralateral ear.

A defining feature of patients with auditory neuropathy is the clearly recognizable waveforms of the TEOAE in the absence of ABR, indicating that the hearing disorder is not brought about by significant dysfunction of the cochlear outer hair cells. Various studies have reported the lack of contralateral suppression of TEOAE in patients with auditory neuropathy, consistent with VIIIth nerve pathology occurring in the contralateral afferent pathway.

Cochlear microphonics and electro-cochleography

Cochlear microphonics are the early components of the ABR generated in the cochlea. They occur in the 0.7–1 ms window post-stimulus and show similar waveform characteristics to the stimulus itself. Typically, this response is cancelled out when performing ABR by using alternate polarity clicks, thereby generating a 'microphonic-free' ABR. Trans-tympanic ECochG indicate that the phase reversal to the click stimulus occurs at the level of the cochlea itself, and therefore the presence of cochlear microphonics is indicative of a preneural response to sound. ECochG is used to measure the summating and action potentials and is most commonly used in the diagnosis of Ménière's disease, when the summating potential to action potential ratio is greater than 30% (in the normal population it is significantly smaller).

Acoustic brainstem evoked responses

ABR are detected by surface electrodes, and are a far-field reflection of electrical activity generated by the VIIIth nerve and brainstem auditory pathways in the 10 s immediately after an acoustic stimulus. Waves I and II are thought to come from generator sites in the distal and proximal sections of the VIIIth nerve, respectively; and III, IV and V from generator sites within the brainstem auditory pathways (Fig. 14.23). Prolongation of the I–III interval can be seen in auditory nerve and cochlear nucleus pathology. Prolongation of the III–V is usually indicated when pathology is sited above the level of the cochlear nucleus, while absent IV and/or V waves are found in cases with involvement of the mid-upper pons.

Inter-aural latency comparisons of wave V are of value in diagnosis of acoustic neurinoma, but may not be useful in detecting brainstem involvement. The sensitivity and specificity of the auditory brainstem response in identifying brainstem lesions depends on the site of lesion, i.e. more caudal intra-axial structured brainstem lesions are identified but the ABR is only moderately sensitive (around 80%) for degenerative disorders or rostral brainstem lesions.

As a diagnostic tool, ABR are of particular value in discriminating between cochlea and VIII nerve or brainstem dysfunction. It has been proposed that the absent ABR of the patient with auditory neuropathy can be explained by the altered temporal synchrony of the auditory brainstem pathway, suggesting that in these patients, auditory nerve and brainstem discharges are not precisely time-locked to the acoustic signal, so that short duration components, i.e. of 1 ms, are cancelled in the averaging process rendering them indistinguishable from background electrical levels.

Early event related potentials: summary

Oto-acoustic emissions are preneural phenomena that reflect the integrity of the outer hair cells of the cochlea, whereas ABR and the summating and compound action potential of the ECochG are tests of neural synchrony. The common stimulus to all these phenomena is the broad spectrum 100 μs pulse. If diagnosticians do not have access to measurement of OAE, patients with auditory neuropathy can be detected by comparison of ABR responses to condensation and rarefaction clicks at 100 μs.

Middle latency response

The middle latency response generator sites are presumed to be within thalamo-cortical pathways to the auditory cortex. There is much inter-subject variability. Most effective measurements are intra-subject comparisons between the electrode effect and the ear effect. Sensitivity and specificity of middle latency responses for central auditory pathology is reasonably good, and the test is therefore valid and objective in assessment of central auditory dysfunction. Sleep and sedation may affect responses.

Cortical-evoked auditory responses

Cortical- or late-evoked auditory responses are the most effective method of defining auditory thresholds at each frequency in a patient who is unable or unwilling to cooperate; they are essential in legal cases, in which non-organic loss should always be considered.

Psychophysical tests

Further transmission of neural impulses via the auditory nerve to the brainstem is followed by auditory projections to higher centres where perceptual registration and cognitive elaboration takes place. These functions are gradually being unlocked by the use of a variety of psychophysical tests. Psychophysical and/or behavioural measures are used to assess patients with a putative lesion of the auditory brain. They can be broadly divided into discrimination tasks, temporal tasks, low redundancy speech tests, dichotic tests and binaural integration tests:

- *Discrimination tasks* of various sound features.
- *Temporal tests*: sequencing tasks, such as gaps in noise, with silence embedded within a noise burst, to assess ability to analyse changes of sound over time.

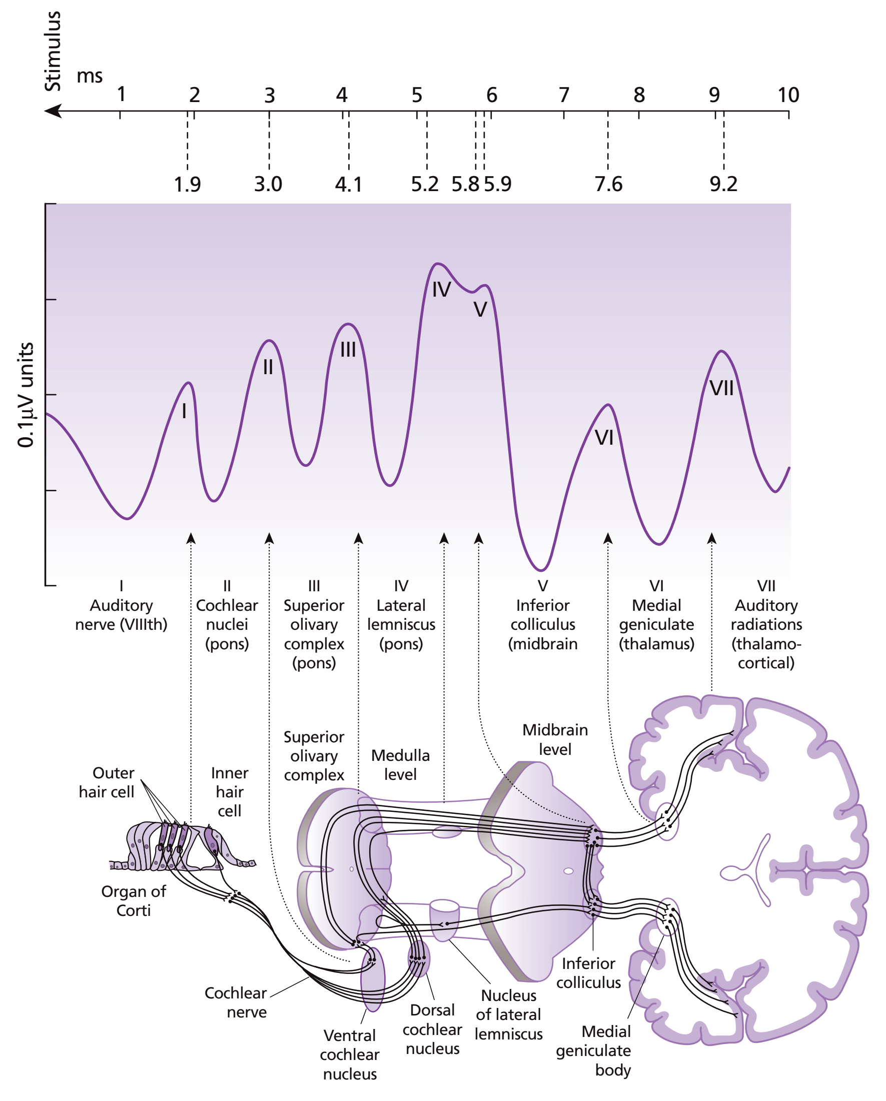
Stimulus
ms
1
2
3
4
5
6
7
8
9
10
1.9
3.0
4.1
5.2
5.8
5.9
7.6
9.2
0.1μV units
I
II
III
IV
V
VI
VII
I
Auditory nerve (VIIIth)
II
Cochlear nuclei (pons)
III
Superior olivary complex (pons)
IV
Lateral lemniscus (pons)
V
Inferior colliculus (midbrain
VI
Medial geniculate (thalamus)
VII
Auditory radiations (thalamo-cortical)
Outer hair cell
Inner hair cell
Superior olivary complex
Medulla level
Midbrain level
Organ of Corti
Cochlear nerve
Ventral cochlear nucleus
Dorsal cochlear nucleus
Nucleus of lateral lemniscus
Inferior colliculus
Medial geniculate body

Figure 14.23 Acoustic brainstem evoked responses showing the series of neurogenic potentials in the 10-s post click stimulus and the putative generator sites in the VIIIth nerve, brainstem and thalamus. (From Duane 1977, with permission.)

- *Monaural low redundancy speech tests*: speech stimuli, presented to one ear, to assess recognition of degraded speech.
- *Dichotic tests*: a different sound is presented simultaneously to each ear.
- *Binaural integration tests*: stimuli presented to both ears, the task requiring the patient to attend to one ear only, or both at the same time, e.g. competing sentence tests, used to assess the listener's ability to synthesize auditory information distributed to both ears, into a single event.

In the dichotic situation, the weaker ipsilateral auditory pathway tends to be suppressed, and neural impulses travel up the contralateral pathway to reach auditory reception areas in the auditory cortex. Contralateral ear effects are observed in cases of auditory cortical involvement, while left ear deficits are observed in lesions involving the interhemispheric pathways, e.g. the corpus callosum. Temporal ordering tasks use non-verbal stimuli in order to assess the auditory processes of feature detection, frequency or duration discrimination. All of these tasks are largely dependent on intact right hemisphere auditory function.

Aetiology of hearing loss

Here the focus is on conditions that present in neurological practice, both adult and paediatric; but there remains considerable overlap between the clinical practice of neuro-otologists, ENT surgeons, audiological physicians and, on occasion, neurologists.

Conductive hearing loss

Disorders of the tympanic membrane and middle ear

Acquired disorders include acute otitis media, chronic otitis media, serous otitis media, aural cholesteatoma and ossicular abnormalities.

Tubo-tympanic disease describes chronic active otitis media unassociated with cholesteatoma. It is characterized by recurrent infections rather than persistent infections and by odourless, rather than offensive discharge. A central TM perforation and a break in the ossicular chain or malleus fixation are regarded as safe, and unlikely to be associated with aural cholesteatoma. Serous otitis media is recognized by an air–fluid level in the middle ear, or a bluish discoloration of the drum. Other effusions into the middle ear include blood (e.g. haemo-tympanum after head trauma) or cerebrospinal fluid (CSF) within the middle ear space.

An aural cholesteatoma is a cyst lined with squamous epithelium, which can arise in ears undergoing long periods of negative middle ear pressure and persisting middle ear infection, i.e. following chronic suppurative otitis media. Cholesteatomatous cysts are likely to begin in the attic and extend into the mastoid antrum. They are filled with cast-off epithelial cell debris and slowly increase in size. They can erode the surrounding bone and produce intracranial complications by eroding through the dura of the middle or posterior fossa, or through the lateral sinus or into the lateral semicircular canal. Aural cholesteatoma can be diagnosed from a history of perforation, chronic foul-smelling discharge from the ear and keratin debris in the pars flaccida area on otoscopic examination. It is potentially serious and requires surgical removal.

Otosclerosis

Otosclerosis is an inherited autosomal dominant hearing disorder, tending to develop in later childhood or adulthood, associated with the *TGBF1* gene. Deposition of bone in the oval window niche leads to fixation of the stapes footplate and a conductive hearing loss. The otosclerotic process can extend to involve the otic capsule, to cause additional sensorineural hearing loss and vertigo.

Glomus tumours

These are jugulo-tympanic paraganglionomas that tend to expand within and traverse the petrous temporal bone by way of the pneumatized air cell tracts. A glomus tumour can present with pulsatile tinnitus; a vascular mass lying behind the TM can sometimes be seen – the setting sun sign. These tumours may also extend into the labyrinth, or present as cranial nerve abnormalities (see Chapter 12).

Cochlear hearing loss

In the developed world interest in sensorineural hearing loss has risen in part because of the earlier detection of infants with profound hearing loss through the newborn hearing screening programmes and in part because of effective prosthetic, pharmacological and genetic interventions.

Genetic hearing loss

In the last two decades there have been enormous strides in the understanding of genetic and environmental causes of hearing loss. Currently, 67 loci for autosomal recessive inheritance of hearing loss have been defined, while 54 for autosomal dominant inheritance have been reported, in addition to mitochondrial mutations and genetic aberrations giving rise to X-linked hearing loss (Hereditary Hearing Loss Homepage http://webh01.ua.ac.be/hhh/). Many of these forms of genetic hearing impairment present either in a non-syndromal or syndromal pattern.

Age-related hearing loss, characterized by progressive deterioration of auditory sensitivity with age, is the leading cause of adult auditory impairment. Until recently it has been attributed to a variety of factors including genetic, nutritional, socio-economic and environmental variables. However, recent work has suggested that this condition may in fact represent inherited late-onset progressive hearing loss, and that specific genes may predispose individuals to environmental triggers affecting various molecular mechanisms underlying changes in auditory function. Specifically, a mitochondrial mutation associated with aminoglycoside-induced hearing loss has been reported.

Autosomal recessive hearing loss

Autosomal recessive hearing loss accounts for approximately 40% of all cases of childhood hearing loss and manifests as stable, profound, congenital/prelingual impairment. There may be marked intra-familial variation in the severity of the loss. Radiology is generally normal. Three recessive loci, *DFNB2*, *DFNB4* and *DFNB12* have been associated with vestibular dysfunction. The genes causing recessive hearing loss have been demonstrated to code for transcription factors, *POU* genes, motor molecules – unconventional myosins myo7A, myo15, gap junction proteins GJB2, GJB3, GJB6, and the ion transporters KCNQ4, and PDS, the Prestin and matrix proteins Tecta and Col11A2. *GJB2* gene encodes the gap junction protein connexin 26, which has been shown to cause 50% of autosomal recessive sensorineural hearing loss in Caucasian and European populations. The most common mutation is 35delG, and the overall carrier frequency of this mutation has been identified as 1:51 in Europe. The prevalence of *GJB2* mutation in autosomal recessive sensorineural hearing loss has led to routine clinical screening for this mutation in families with an autosomal recessive presentation.

Autosomal dominant hearing loss

Autosomal dominant sensorineural hearing loss is uncommon in prelingual profound hearing impairment, but is well recognized in families with hearing loss of various configurations, differing ages of onset and differing rates of progression. Commonly there is good correlation between phenotype and genotype, and vestibular involvement has been identified in *DFNA9* and *DFNA11*. A wide variety of different audiometric configurations have been reported, including unilateral loss, low-frequency sensorineural hearing loss both of stable and progressive type, mid-frequency loss, high-frequency loss, and associated with progressive vestibulo-cochlear dysfunction.

Syndromic hearing loss

More than 100 syndromes have been reported with associated hearing impairment; the more common, with their predominant features, are shown in Table 14.14. Many of these present in child-

Table 14.14 Inheritance, predominant features, auditory and vestibular abnormalities and CNS findings in syndromes associated with hearing loss. (From Luxon 2007, with permission.)

Syndrome	Mode of inheritance	Predominant features	Auditory and vestibular features	CNS status
Treacher–Collins	AD	Mandibulofacial dysostasis	Severe dysplasia middle and internal ear (A + V)	N
Branchio-otorenal	AD	Branchial cysts/fistulae Structural +/– functional renal abnormalities	Anomalies of external ear CHL 20%, SNHL 30%, Mixed 50%	N
CHARGE	Occasional AD Rare AR Most sporadic	**C**oloboma, **h**eart defect, **a**tresia of choanae, **r**etarded growth and development, **g**enital hypoplasia, **e**ar anomalies	Structural labyrinth (A + V) dysplasia VIII nerve involvement Absent semicircular canals SNHL +/– CHL	Impaired IQ and development
Usher's	AR	Retinitis pigmentosa	Type I: A + V failure Type II: A failure Type III: Variable	N
Alstrom's	AR	Pigmentary retinopathy Diabetes mellitus Obesity	SNHL	N
Apert's	Mainly sporadic. Some AD	Craniosynostosis + oral manifestations. Brachydactyly	CHL ME anomalies	Frequent low IQ CNS manifestations
Crouzon's	AD	Craniosynostosis Shallow orbits Ocular proptosis	CHL ME anomalies	Generally N
Osteogenesis imperfecta	AD	Blue sclera Opalescent teeth Deformities of long bone and spine, hyperextensibility	Type 1 Mild CHL >10 years of age Progressive mixed hearing loss	Generally N
Stickler's	AD	Flat midface and cleft palate High myopia and retinal detachment and cataracts Arthopathy Spondylo-epiphyseal dysplasia	Progressive SNHL	N
Wildervanck's	Sporadic	Fused cervical vertebrae Abducens palsy and retracted globe	SNHL, CHL or mixed in ~30%. Vestibular failure common	Usually N
Alport's	Usually X-linked dominant, rarely AR	Progressive glomerulonephritis Bilateral anterior lenticonus and macular flecks or peripheral coalescing flecks	Progressive SNHL in >10 years in approximately 50% of cases	Usually N
Jervell–Lange–Nielsen	AR	Prolonged Q-T interval Fainting spells/sudden death	Profound SNHL Scheibe anomaly	N
Pendred's	AR	Goitre	Mondini defect Dilated vestibular aqueduct Severe-profound SNHL Vestibular failure 30%	N
Mucopolysaccharidoses: Hurler's Hunter's	AR except Hunter's syndrome which is X-linked	Growth failure. Death <10 years Craniofacial dysmorphism Lysomal storage Excess excretion of dermatomes and heparin sulphates Severe form → death at 4–14 years Mild form → less severe than Hurler's syndrome	Progressive CHL Central auditory dysfunction Mixed HL in ~50%	Impaired IQ and development
Refsum's	AR	Retinitis pigmentosa HMSN (Cardiac enlargement/dysrhthymias Icthyosis)	Progressive SNHL Vestibular function: normal	Anosmia Progressive weakness + sensory neuropathy, cerebellar signs
Down's	Trisomy 21	Short stature Dysmorphic facial features Hypotonia Single palmar crease Cardiac anomalies Delayed mental development	Abnormal external ear morphology CHL and/or SNHL in majority	Impaired IQ and development

A, auditory; AD, autosomal dominant; AR, autosomal recessive; CHL, conductive hearing loss; HL, hearing loss; ME, middle ear; SNHL, sensorineural hearing loss; V, vestibular.

hood, but hearing loss associated with certain syndromes can progress or indeed become apparent in adult life.

Usher's syndrome

This congenital disorder occurs in about 1 in 25,000 live births and is the most common condition causing both deafness and blindness. It accounts for 5% of deafness in children. The condition is conventionally divided into three forms (Usher types I–III) which vary in severity and symptomatology. Symptoms include sensorineural deafness and lack of balance, learning disability, cataracts, glaucoma and progressive retinitis pigmentosa. It has 12 loci and 9 genes are currently identified.

Pendred's syndrome

This is an autosomal recessive disorder caused by a mutation of the *SLC26A4* gene and accounts for over 5% of deafness present at birth. The deafness is sensorineural in nature, although there are often associated abnormalities of the middle ear. Goitre develops in late childhood or early adult life, usually without thyroid hormonal changes. There may be associated learning difficulty.

Waardenburg's syndrome

This describes a group of rare inherited disorders characterized by sensorineural deafness, defects in neural crest structures and abnormalities of pigmentation. There are four distinct types. Most cases are inherited in an autosomal dominant fashion, although some type II and IV cases are autosomal recessive. Symptoms and severity vary considerably and differ in different types. Defects in at least eight genes have been identified including the *PAX*-3 gene. Absence of melanocytes causes pale or brilliantly blue eyes, complete or sectoral heterochromia, a forelock of white hair, premature greying of the hair and patches of depigmentation on the skin. Midline defects include hypertelorism, cleft lip or palate, a prominent broad nasal root, low hairline and eyebrows that touch in the middle, and disorders of spinal development. Other neurological, skeletal and gastrointestinal abnormalities can occur.

Alport's syndrome

This is a rare inherited disorder which occurs in 1 in 50,000 persons. Typically, it is caused by mutations in the *COL4A5* gene on the X chromosome, but sometimes by the autosomal *COL4A3* and *COL4A4* genes. The condition is characterized by renal failure and deafness, but also by ocular manifestations which are usually asymptomatic. The renal failure develops in early adult life (Alport's syndrome is a common cause of renal failure in young adults) and is usually the predominant symptom.

Metabolic disease

Diabetes mellitus

A plethora of literature exists on diabetes mellitus as an aetiological factor for hearing loss but, despite this, controversy remains, and there is no clear evidence indicating whether or not patients with diabetes mellitus have auditory and/or vestibular abnormalities as a consequence of neuropathy, angiopathy or both pathologies. Recent genetic studies have defined the relationship of diabetes and hearing loss in mitochondrial mutations and in mutations of the *WFS1* gene in the Wolfram syndrome of non-syndromic hearing impairment, diabetes mellitus and psychiatric disease.

Renal failure

Hearing loss is a common finding in patients with renal failure. Ototoxicity from both disease and drugs and axonal uraemic neuropathy have all been suggested as possible factors, while both dialysis and renal transplantation have been reported to be associated with recovery of hearing impairment. Recent work using ABR has supported a possible underlying neuropathy with retrocochlear involvement.

Drugs

Many drugs produce ototoxicity, with the most common being chloroquine, loop diuretics, aminoglycosides and salicylates. Platinum-based chemotherapeutic agents, in addition to the aminoglycosides, have been shown to damage the hair cells of the inner ear, while vincristine sulphate has been shown to produce bilateral cochlear nerve damage. Salicylates, which are highly concentrated in the perilymph, may interfere with the enzymatic activity of the hair cells or the cochlear neurones, or both. Thalidomide has been demonstrated to produce aplasia of the VIIIth nerve in association with a Michel aplasia of the inner ear. The common drug-induced deafness encountered in neurological practice is caused by intrathecal streptomycin used for the treatment of meningitis, which itself can also cause deafness. Other aminoglycosides, such as gentamicin, can also cause deafness, although typically they cause bilateral vestibular failure. Care needs to be taken in their prescription and administration; blood level estimations are helpful in preventing ototoxicity.

Acoustic trauma

Hearing loss may result from acoustic trauma in the form of noise, physical trauma or iatrogenic damage from drugs, radiotherapy and surgery.

Noise

Noise-induced permanent threshold shift is one of the most common and most easily preventable causes of sensorineural hearing loss. It is commonly the consequence of hazardous occupational and/or recreational exposure to noise, and may also be associated with acoustic trauma, e.g. gunfire and explosions. Characteristically, the maximal loss is at 4000 Hz, with a notched configuration to the audiogram. With time, the adjacent frequencies gradually deteriorate, but it is rare for a hearing loss greater than 70 db to be the result of occupational noise exposure. The diagnosis of noise-induced hearing loss is by exclusion of other causes, but because aetiology cannot be ascertained in up to two-thirds of patients with sensorineural hearing loss, this is a dilemma. The American College of Occupational Medicine (1989) have devised clear diagnostic criteria for occupational noise-induced hearing loss. A history of noise exposure should be sought in all cases of high-frequency sensorineural hearing loss.

Barotrauma

Acute barotrauma associated with diving, depressurization in aircraft and explosions may give rise to tympanic membrane haemorrhage into the middle ear, with conductive hearing loss or perilymph fistula which is commonly associated with auditory and vestibular symptoms.

Head injury

Head injury may lead to middle ear, inner ear, VIIIth nerve and/or central auditory loss. Trauma can cause labyrinthine concussion and fractures of the petrous temporal bone. Fractures are either longitudinal, extending through the middle ear cavity with concomitant conductive hearing loss, or transverse with section of the VIIIth nerve, facial paralysis and haemotympanum – frequently associated with a profound sensorineural loss and acute vertigo.

In mild and moderate head injuries, some 40% of patients complain of hearing loss and/or tinnitus; the prevalence of auditory abnormalities in these cases on detailed testing is around 50%. The most common configuration of sensorineural hearing loss, when there is no fracture, is a bilateral high-tone sensorineural hearing loss. Other configurations, including asymmetric and unilateral loss, may also be found. A notch-shaped hearing loss at 4 kHz has also been reported.

Autoimmune disorders

Autoimmune disorders are not uncommon causes of deafness (Table 14.15).

Autoimmune inner ear disease

Autoimmune inner ear disease (AIED) refers to a presumed autoimmune condition in which there is sudden or rapidly progressive hearing loss in the absence of any other neurological or systemic immunological abnormalities. Although AIED seems to be caused by autoimmune attack on inner ear proteins, no antigen has yet been identified. Immunosuppressive therapy can prevent the progression of deafness. Typically, the hearing loss is bilateral, progressive over several months and associated with vestibular symptoms. There are no specific laboratory tests. Treatment, particularly if started early, can be very effective. Steroids (both intratympanic and orally administered), methotrexate, plasmapheresis, cyclophosphamide or azathioprine are used. There is often a fluctuating course, and many responders to treatment require long-term immunosuppression. The prognosis for hearing without therapy is uniformly poor. In those who respond to immunosuppression the outlook for hearing is good.

Table 14.15 Autoimmune syndromes associated with hearing loss. (From Overell & Lindhall 2004, with permission.)

Condition/syndrome	Neuro-otologic syndrome	Associated findings	Epidemiology	Laboratory markers/diagnostic tests
Cogan's syndrome	'Ménière-like': attacks of vertigo, nausea, tinnitus, and hearing loss	Eye inflammation (keratitis, scleritis, conjunctivitis, uveitis, retinal vasculitis); systemic vasculitis in 10%	Young adults and older children (median 25 years)	Neutrophilia, raised ESR/CRP, MRI enhancement of vestibulocochlear structures
Wegener's granulomatosis	Usually conductive hearing loss; often have otitis media; SNHL reported, but usually as part of mixed picture	Rhinorrhoea and sinusitis; pulmonary, renal, joint manifestations; peripheral nervous system involvement	40–50 years; males and females equally affected	Raised ESR/CRP, raised ANCA (proteinase 3), granulomatous infiltration on MRI, biopsy
Polyarteritis nodosa	Rapid SNHL	Systemic vasculitis (kidney, gut); constitutional symptoms; mononeuritis multiplex	Male > female; older age of onset	Leucocytosis, raised ESR, visceral angiography, organ/nerve/muscle biopsy
Systemic lupus erythematosus	Subacute SNHL; often subclinical (NSAIDs and antimalarials may complicate picture – both may cause SNHL)	Skin, joint, renal, neuropsychiatric; constitutional symptoms	Female > male (5 : 1); age 15–40 years	Raised ESR, ANA, dsDNA antibodies, antiphospholipid antibodies, complement consumption
Sjögren's syndrome	Often subclinical	Dry eyes, dry mouth; Raynaud's and joint symptoms; neuropathies (axonal, sensory-ataxic, trigeminal)	Female > male	ANA, Ro, La, Schirmer's test, lip biopsy

ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; NSAIDs, non-steroidal anti-inflammatory drugs; SNHL, sensorineural hearing loss.

However, there are no uniform criteria for diagnosing immune-mediated inner-ear disease, and evidence-based diagnostic criteria and assessment methods remain to be established.

Cogan's syndrome

This is a rare, presumed autoimmune disorder that develops usually in children and young adults in the aftermath of an upper respiratory tract infection. No infectious agent has been conclusively identified as a cause, although an association with *Chlamydia* has been reported in several studies. The condition affects the eye and the ear. Inflammatory ocular manifestations include keratitis, iritis, scleritis or conjunctivitis. Vestibular symptoms include balance disorders, dizziness and tinnitus and these can progress rapidly to total bilateral deafness. There are also systemic manifestations, including lymphadenopathy, night sweats and cardio-respiratory involvement including aortitis, aortic valve insufficiency, pericardial effusion and coronary arteritis, pleuritis and myocardial infarction. Vasculitis can cause major organ damage and occasionally be fatal. The clinical context, the rapidly developing bilateral sensorineural hearing loss, ocular manifestations and vasculitic features, and the high ESR suggest the diagnosis.

Vogt–Koyanagi–Harada syndrome

Vogt–Koyanagi–Harada (VKH) syndrome is a rare condition characterized by bilateral uveitis with cutaneous lesions (vitiligo, alopecia and poliosis), neurological features (CSF pleocytosis) and auditory abnormalities. It is essentially a disorder of melanocyte-containing organs, and occurs more frequently in individuals with darker skins. It is more common in females and usually presents in children or young adults. The pathogenesis is unclear, although there is a statistically significant association with HLA-DR4. There is often a prodromal period of headache, vomiting and low-grade fever. Classically, VKH progresses in three phases: initially symptoms are those of a meningo-encephalitis, and deafness can be a predominant symptom; in the second phase, the ophthalmic-auditory phase, there is uveitis, diminution of visual acuity and eye pain; and in the third (convalescent) phase, cutaneous signs develop when the uveitis has subsided, usually within 3 months of the onset. Treatment of VKH is with steroids and other immunosuppressive agents.

Susac's syndrome

Susac's syndrome is a rare micro-angiopathy resulting in encephalopathy, retinopathy and hearing loss, and is assumed to have an autoimmune basis (Chapters 4 and 25). It occurs mainly in young adult women and has an acute or subacute presentation. Sensorineural hearing loss is often the presenting feature, associated usually with tinnitus and vestibular disturbance. The hearing loss can be unilateral or bilateral, and sometimes subtle. The encephalopathy causes prominent headache, personality change, paranoia, confusion and cognitive impairment. The retinopathy typically causes retinal branch occlusion and sectoral blindness. The differential diagnosis includes multiple sclerosis and acute demyelinating encephalomyelitis. There are no definitive diagnostic tests; brain MRI shows multiple T2 high intensity lesions, reminiscent of MS. Treatment is usually with immunosuppressive agents although the pathogenesis has not been conclusively shown to be immunologically mediated.

Other autoimmune conditions associated with deafness

Other presumed autoimmune conditions include sensorineural deafness amongst their complications. These are systemic lupus erythematosus (SLE), ulcerative colitis, scleroderma, polyarteritis nodosa, Sjögren's syndrome, giant cell arteritis and Wegener's granulomatosis. Treatment is of the underlying condition.

Behçet's syndrome

In Behçet's syndrome (Chapter 25) about one-third of cases have predominantly high-frequency hearing loss, with normal ABR. Subtle eye movement abnormalities such as dysmetric saccades and smooth-pursuit dysfunction may be seen. Auditory loss of cochlear type, and vestibular dysfunction also occur.

Retro-cochlear hearing disorders

Retro-cochlear hearing loss is either genetic, acquired congenitally or acquired postnatally (Tables 14.16–14.18). Remember that genetic causes can present with hearing impairment in adult life.

An almost invariable complaint of patients with retro-cochlear damage (auditory neuropathy) is that hearing difficulties are worse with speech than with environmental sound; using a telephone causes particular difficulty. Patients complain that whereas they can identify speech sounds and the language used, they cannot understand words. These difficulties are always more marked in noisy environments, with competing signals. An auditory neuropathy can be thought of as causing a 'time-smear' of sound. The severity of hearing impairment varies; this can be either transient, intermittent, stable or deteriorating.

Genetic or congenitally acquired

In addition to genetic dysfunction of the cochlea, recent studies have defined genetic abnormalities giving rise to auditory neuropathy. A number of children have autosomal recessive auditory neuropathy without any other abnormality, and both linkage studies and mutation analysis have identified the otoferlin gene as being responsible for this type of hearing loss. Mutations in *12SrRna* gene are also associated with auditory neuropathy. Auditory neuropathy may occur with common neurological syndromes, such as Charcot–Marie–Tooth disease (Chapter 9).

Charcot–Marie–Tooth disease

In 1951, Denny Brown reported a case of hereditary sensorimotor neuropathy (HSMN) with deafness; at autopsy, 'thin auditory nerves' were found. Hearing loss has subsequently been reported in many HSMN cases.

Sensorineural hearing loss occurs in Charcot–Marie–Tooth disease (Chapter 9) type 1a and hereditary neuropathy with

Table 14.16 Genetic/congenitally acquired retro-cochlear hearing disorders. (From Davies 2008, with permission.)

Genetic	Non-syndromal	Non-syndromal recessive auditory neuropathy due to mutations in the otoferlin gene Delayed maturation of auditory pathways in neonates	
Genetic	Syndromal	With peripheral neuropathy	Hereditary sensorimotor neuropathy, e.g. Roma (gypsy) families Friedreich's ataxia Neurofibromatosis type 2 Refsum's disease
Genetic	Syndromal	Without peripheral neuropathy	Arnold–Chiari Usher's syndrome (see above) Mitochondrial myopathies: MELAS Chronic progressive external ophthalmoplegia Mohr–Tranebjaerg's syndrome (deafness/dystonia peptide) Skeletal syndromes: Branchio-otorenal Wildervanck's Bone dysplasias: Osteopetroses Hyperostosis cranialis Cammurati–Engelmann's disease Gaucher's
Congenital/toxic/metabolic			Perinatal risk factors: Asphyxia Respiratory distress syndrome Low birth weight Cerebral palsy Hyperbilirubinaemia Thalidomide

MELAS, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes.

Table 14.17 Clinical features of mitochondrial syndromes associated with deafness. (From Overell & Lindhall 2004, with permission.)

Condition/syndrome	Neuro-otological syndrome	Main clinical features	Additional features	Epidemiology	Laboratory markers
MELAS	Cochlear origin; symmetric gradual onset SNHL	Encephalopathy (seizures ± dementia); stroke-like episodes; mitochondrial myopathy	Short stature; normal early psychomotor development; recurrent headache and vomiting	Usually first decade; sometimes 10–40 years	Ragged red fibres on muscle biopsy; increased lactate
MERRF	Symmetric gradual onset SNHL	Myoclonus; epilepsy; cerebellar syndrome; myopathy	Short stature; dementia; optic atrophy; cardiomyopathy; Wolff-Parkinson-White syndrome; peripheral neuropathy	Usually childhood onset, but may be adults	Ragged red fibres on muscle biopsy; increased lactate
KSS	Symmetric gradual onset SNHL	Retinitis pigmentosa; ophthalmoplegia	Cardiac conduction block; cerebellar syndrome; short stature; impaired intellect	Onset <20 years; majority are sporadic	Ragged red fibres on muscle biopsy; increased lactate, raised CSF protein

CSF, cerebrospinal fluid; KSS, Kearns–Sayre syndrome; MELAS, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibres; SNHL, sensorineural hearing loss.

Table 14.18 Acquired retro-cochlear hearing disorders. (From Davies 2008, with permission.)

Acquired infection	Viral	Herpes zoster/herpes simplex: Ramsay-Hunt syndrome Bell's palsy CMV, varicella, mumps HIV/AIDS
	Bacterial Fungal/protozoan Spirochaetal	Basal meningitis Pneumococcal Meningococcal Haemophilus Tuberculosis Cryptococcosis Coccidiomycosis Toxoplasmosis Syphilis, borrelia
Immune-mediated	Post-infective	Guillain–Barré
	Vasculitic/granulomatous	SLE, rheumatoid, sarcoid, Behçet's syndrome
Demyelination	Multiple sclerosis VIIIth nerve Brainstem	
Neoplasia/neoplasia related	Vestibular schwannoma Meningioma Cerebellopontine angle lesions Carcinomatosis Malignant meningitis Radiotherapy	
Metabolic/toxic	Uraemia Paget's disease Organic mercury Cisplatin Superficial siderosis	
Vascular	?Migraine Posterior inferior cerebellar artery syndrome Posterior fossa aneurysms AVM Vascular loops	

AVM, arteriovenous malformations; CMV, cytomegalovirus; SLE, systemic lupus erythematosus.

liability to pressure palsies (HNPP). In the latter, half are thought to have the common PMP22 deletion, and half a PMP22 frameshift mutation. Substantial sensorineural hearing impairment occurs in all three groups with dome-shaped losses with both a mild to moderate low-frequency and high-frequency loss. In HNPP cases, data suggests excessive presbyacusis.

In one series of 70 cases of auditory neuropathy, no aetiology was identifiable in 40%. The auditory neuropathy was typically bilateral, affecting sexes equally. Polyneuropathy, principally forms of distal HSMN, was identified in 26%. One Roma family from Slovenia was shown to have a mutation on chromosome 8q24. Inheritance was autosomal recessive. Within this Roma family, polyneuropathy occurred first, with hearing loss developing in later years; some cases had bilateral vestibular failure.

Neurofibromatosis type 2

This autosomal dominant genetic disorder, associated with acoustic neuromas, causes retro-cochlear hearing loss. Neurofibromatosis type 2 (NF2) is 10 times less common than NF1 and occurs in 1/30,000–40,000 people. Mutations are found in the NF2 gene (neurofibromin 2; merlin), a tumour suppressor gene located on chromosome 22. Over 50% of NF2 cases are a result of new mutations. The clinical manifestations include peripheral neurocutaneous manifestations (café-au-lait spots and peripheral nerve neurofibromas), ocular abnormalities (juvenile posterior subcapsular lens opacity, retinal hamartomas and optic nerve sheath meningiomas) and both CNS and spinal tumours. CNS tumours include meningiomas (often multiple), vestibular schwannomas (acoustic neuromas), schwannomas in other locations, optic nerve gliomas, ependymomas and neurofibromas. Ninety per cent of NF2 patients have vestibular schwannomas, often bilateral; 50% develop meningiomas or other cranial nerve tumours, 40% develop spinal ependymomas or astrocytomas and 90% ocular manifestations, when examined in detail.

Symptoms from a vestibular schwannoma can develop at any age, although rarely over 50 years, and the condition usually presents in the second or third decade (see below). Deafness is often the first symptom in adult NF2 patients; in children ocular signs are more common. Speech recognition may be disproportionally poor, given the level of hearing loss. As genetic testing and screening with MRI or neurophysiological tests become more widespread, cases can be picked up in an asymptomatic stage. If no manifestations have occurred by the age of 30 years in those with a family history, the disease is unlikely to occur.

The type of genetic defect influences prognosis: nonsense or frameshift mutations generally cause severe disease, and missense mutations, in-frame deletions or large deletions cause milder disease. Severity varies in those with splice site mutations. The growth rate of VIIIth nerve tumours in NF2 is variable; for very slow growing tumours there is a case for non-operative management. However, the majority of patients with NF2 will develop severe deafness, and some will also become blind. Mean survival after diagnosis is some 15 years and the mean age of death in NF2 around 40 years.

Friedreich's ataxia

Friedreich's is the most common inherited ataxia (Chapter 16), and is frequently caused by a large expansion of an intronic GAA repeat, resulting in decreased expression of the gene product frataxin. The condition is usually inherited in an autosomal recessive pattern, and as frataxin is a mitochondrial protein, it suggests that dysfunction in Friedreich's ataxia is caused by a mitochondrial abnormality. Hearing impairment as an associated but unusual feature. One study has reported abnormal ABR with normal oto-acoustic emissions, suggesting auditory neuropathy in two cases of Friedreich's ataxia. Hearing loss in association with dominantly inherited late-onset cerebellar ataxia has also been reported.

Refsum's disease

Refsum's disease (Chapter 18) is characterized by defective peroxisomal alpha oxidation of phytanic acid, with clinical features of retinitis pigmentosa, polyneuropathy, anosmia and hearing loss. Adult Refsum's disease is a recessive disorder of the phytanoyl CoA hydroxylase, *PAHX* gene on chromosome 10p30. Although hearing loss in Refsum's disease is common, only a few detailed assessments exist. One report demonstrates that seven of nine adults with Refsum's had a mild to moderate sensorineural hearing loss, predominantly of high-frequency type, and subtle auditory nerve involvement was identified in seven on the basis of ABR.

Mitochondrial disorders

Mitochondrial conditions have a propensity to cause sensorineural hearing loss (Table 14.17).

Children with mitochondrial encephalopathies including Kearns–Sayre syndrome (KSS) and MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes) tend to have progressive hearing loss of both cochlear and retro-cochlear origin. No correlation between the type and severity of hearing loss and number or severity of other clinical neurological findings is found. In one study of of adult patients with 3243A < G mutation, 13 of 16 had a sensorineural hearing loss that was progressive, and both this feature and the severity were correlated with the mutation heteroplasmy in muscle at entry and at end of follow-up. Sensorineural deafness is also a feature of MERRF (myoclonic epilepsy with ragged red fibres) as well as the other less common syndromes (Chapter 9).

There are a range of other inherited disorders in which deafness is part of the spectrum and which may involve mitochondrial dysfunction. These conditions include nuclear mitochondrial conditions such as Mohr–Tranebjaerg syndrome, an X-linked recessive condition, comprising sensorineural hearing loss with onset in childhood, followed by progressive dystonia, spasticity, dysphagia, and optic atrophy in adult life. This is caused by mutations in the DDP (deafness/dystonia peptide) gene, thought to result in mitochondrial dysfunction.

Inherited muscle disorders

Inherited muscle disorders can be associated with hearing loss, including facioscapulohumeral dystrophy and myotonic dystrophy. In this latter condition, the hearing loss is reported to resemble 'precocious presbyacusis', or an excessive high-frequency hearing loss characteristic of presbyacusis, and genetic anticipation. In addition, a significant increase in the I–V interpeak interval of ABR was noted, suggesting a retro-cochlear component.

Acquired retro-cochlear hearing disorders (Table 14.18)

Infections

Bacterial, viral and mycotic infections may give rise to hearing impairment by direct invasion, blood-borne transmission or via CSF.

Viral infections

Sudden sensorineural hearing loss in adults is often presumed to be viral in origin. Detection of mumps virus in the perilymph after sudden-onset deafness, and circumstantial evidence suggests that sudden hearing loss may be associated with a variety of viruses. The most common condition is the Ramsay-Hunt syndrome, characterized by facial palsy, hearing loss, and characteristic herpetic vesicles around the pinna and in the external auditory meatus. Sensorineural hearing loss occurs in half to two-thirds of cases and is the result of cochlear or retro-cochlear involvement.

HIV/AIDS and syphilis

A variety of auditory abnormalities have been reported in HIV infection, ranging from conductive to sensorineural hearing loss, with mild audiometric changes, abnormalities in ABR and central auditory dysfunction. One study of HIV cases in South Africa revealed prevalence of hearing impairment of 23%, but the authors concluded that hearing loss may have been associated with opportunistic infections such as otosyphilis, cytomegalovirus or streptococcal meningitis, or treatment.

In otosyphilis, various presentations are seen, including sudden sensorineural hearing loss and a pattern suggestive of Ménière's disease. Importantly, this is one form of treatable progressive sensorineural hearing loss. Check syphilitic serology in anyone with unexplained sensorineural hearing loss; this is particularly the case in HIV-positive patients. Treatment of otosyphilis with penicillin and corticosteroids improves tinnitus and vertigo in some cases. Labyrinthine involvement is more common in late acquired syphilis than in congenital syphilis.

Bacterial meningitis

Sensorineural hearing loss in children during or following bacterial meningitis, including TB, is well known, with prevalence of 5–30%. There is little evidence that any single bacterial infection causes greater loss of hearing, either in frequency or degree. Treatment with antibiotics and adjuvant corticosteroids reduces fatalities and also lowers rates of severe hearing loss and other long-term neurological sequelae.

Lyme disease

Lyme disease (*Borrelia burgdorferi* infection) causes a spreading erythematous rash on the trunk followed by meningo-radiculitis and hearing loss. Elevated antibodies to *Borrelia* antigen have been found in 17% of 98 subjects with a unilateral sudden or fluctuating sensorineural hearing loss. Treatment with intravenous penicillin results in improvement of high-frequency hearing loss in some cases.

Alcohol

Extensive degeneration of both myelinated and unmyelinated nerve fibres in the cochlear and the vestibular divisions of the VIIIth nerve have been reported in chronic alcoholic patients with severe polyneuropathy. However, cranial nerve involvement is rare in chronic alcoholic neuropathy; it has been suggested that this is related more to malnutrition than to a direct toxic effect of alcohol.

Extrinsic and intrinsic tumours of the cerebellopontine angle

Cerebellopontine angle (CPA) tumours present commonly with retro-cochlear hearing loss: these include cerebellar medulloblastoma, vestibular schwannoma, meningioma, cholesteatoma, ependymoma, glomus jugulare tumour and metastasis. MRI will usually identify these tumours. Cerebellar medulloblastomas are common in childhood, where they tend to be midline; in adults these tumours tend to be located laterally and can present as CPA lesions. Malignant meningitis and paraneoplastic syndromes can also present with hearing loss (Chapter 20).

Vestibular schwannoma

The prevalence of vestibular schwannoma is about 1 in 100,000 persons, with a peak incidence in the fifth and sixth decades. Vestibular schwannomas account for 10% of intracranial tumours, and more than 75% of CPA lesions. Males and females are equally affected. About 10% of cases occur in patients with NF2 (see above) or much less commonly in NF1. Ninety per cent of cases appear to develop spontaneously. These tumours tend to be unilateral, arising from the vestibular portion of the VIIIth cranial nerve just within the internal auditory canal. The tumour grows slowly, extending into the CPA. The earliest features are sensorineural hearing loss (50%), tinnitus (21%), dizziness (9%) and rotary vertigo (5%). Eighty per cent of patients report tinnitus at some point. Later symptoms resulting from compression of adjacent structures include ipsilateral facial weakness, ipsilateral facial sensory loss, ataxia, headache, vomiting and signs of raised intracranial pressure (Chapters 12 and 20).

Although most of these tumours arise on the superior division of the vestibular nerve, the most common presenting features are deafness and tinnitus. In all patients with unilateral sensorineural hearing impairment, asymmetric bilateral sensorineural loss or unilateral tinnitus, it is essential to exclude a small vestibular schwannoma by detailed MRI.

Multiple sclerosis

About 5–10% of MS patients experience significant hearing loss, but subtle hearing loss is more common. The presentation of MS with acute hearing loss is rare. MS plaques have been identified in the VIIIth nerve root entry zone, cochlear nucleus and in the pons. Serial MRI has shown the progress of plaques within the ventral cochlear nucleus, near the VIIIth nerve entry zone, in MS patients with sudden hearing loss. Hearing loss typically improves.

ABR audiometry has been used for nearly 30 years to investigate cases with a single MR lesion suggestive of MS, in order to detect other sites of demyelination. The first study in this area showed that in MS patients, a delayed wave V was the most consistent abnormality. This ABR abnormality correlates with clinical evidence of a brainstem lesion resulting from MS over 75% of cases, but ABR abnormalities are also present in over half of those without clinical brainstem signs.

Sarcoidosis

Bilateral deafness is one feature of neurosarcoidosis (Chapter 25), which can present with cranial nerve dysfunction, typically bilateral facial nerve lesions, including the auditory nerve in about 5% of cases. The deafness is usually of VIIIth nerve origin, although cases are described of granulomatous processes causing necrosis of the incus and encasing the chorda tympani. Treatment of the deafness is with conventional immunosuppressive agents; there is one case report of effectiveness of infliximab.

Vascular disease

Stroke, both haemorrhagic and ischaemic, can cause hearing disorders at many levels within the brain, although these are rare. Cavernomas in the brainstem can sometimes cause deafness, either by small haemorrhages or increase in size.

Aneurysms of the anterior inferior cerebellar artery (AICA) constitute less than 1% of all intracranial aneurysms with those of the distal portion (d-AICA) accounting for less than 0.1%. Because of the proximity of the d-AICA to the CPA and the VII–VIIIth nerve complex, aneurysms can mimic vestibular schwannoma, with auditory symptoms – tinnitus and hearing loss. Neuro-otological features related to AICA aneurysms depend on the arterial segment involved, and the relation to the CPA and IAM. Mechanisms include brainstem compression, rupture and post-embolization infarction.

Posterior circulation ischaemia

Sudden deafness occurs following inferior collicular infarction, vertebral artery dissection, infarction of the anterior–inferior cerebellar artery and, rarely, migraine. In one study, 8% of 364 cases of vertebro-basilar insufficiency demonstrated sensorineural hearing loss, the majority (27) being unilateral. Vertigo was associated with hearing loss in most cases. Approximately 50% showed a cochlear type of hearing loss, with approximately half improving over 1 year.

Pontine vascular lesions typically have the greatest effect on hearing. Two overlapping syndromes are recognized: inferior pontine and lateral pontine. Both comprise ipsilateral facial palsy, hearing loss, loss of taste in the anterior two-thirds of the tongue with loss of lateral conjugate gaze. In the lateral pontine syndrome there is also facial sensory loss.

Vascular loops

Whether or not vascular loops compress the VIIIth nerve, to produce vestibular or auditory symptoms is a matter of much debate. Vascular loops crossing over the VIIIth nerve are a normal variant. However, one study of 47 patients with unexplained tinnitus identified that high-resolution MRI T2 weighted images showed a significantly higher number of vascular loops in the internal auditory canal in patients with arterial pulsatile tinnitus than those with non-pulsatile tinnitus; correlation between tinnitus and hearing loss was found. This remains a controversial area.

Superficial siderosis

Superficial siderosis is a rare disorder (Chapter 16). Symptoms include sensorineural deafness (95%), cerebellar ataxia (88%) and pyramidal signs (76%), dementia (24%), bladder disturbance (24%), anosmia (in >17%), aniscoria (>10%) and sensory signs (13%). Other less common symptoms are oculomotor palsies, neck or backache, bilateral sciatica and lower motor neurone signs. Males are more often affected (3 : 1) and the age of onset ranges from the second to decade to later life. Clinical features appear to be caused by chronic subarachnoid haemorrhage. The source of bleeding can be a dural arteriovenous malformation or fistula, dural cyst, other dural pathology, vascular tumour or unknown. Superficial siderosis is insidious in onset and slowly progressive and, if untreated, results in severe disability and premature death. Diagnosis is confirmed by CSF examination, which shows various breakdown products of haemoglobin, and by MRI, which shows a prominent black rim around posterior fossa structures and sulci on T2 imaging, caused by the paramagnetic properties of haemosiderin. Treatment is identification and ablation of the source of bleeding, if this is possible.

Auditory processing disorders

Auditory processing disorders (APD) can manifest in both children and adults with difficulties with word recognition, environmental sounds or music and with uncertainty about what an individual hears, despite the presence of normal hearing thresholds. Patients may experience difficulties listening in a background of noise or with people conversing, difficulties in understanding degraded or rapid speech, following oral instructions, localizing sounds or with the perception of music. They may also have language and other disorders, professional and academic problems and behavioural, emotional, social and other difficulties.

A detailed history of the auditory complaints is vital. First, this is so because patients may deny the presence of hearing complaints, unless questioned in detail – they do not always attribute difficulties to hearing problems. Secondly, features of auditory complaints may help define the diagnosis, e.g. in cases of cortical deafness, in which the patient has abnormal hearing thresholds because of bilateral auditory cortex lesions, and in auditory agnosias, of speech, music and environmental sounds, which may isolated or in combination. Thirdly, identification of specific auditory complaints (e.g. specific pitch difficulties or music-related problems) guides the choice of tests and provides some clues to the site of the lesion.

Aetiology of APD

There are no robust epidemiological data. However, APD is believed to affect 7% of children and prevalence may be even higher in adults. Disordered auditory processing may occur in the presence of the following:

- Genetic causes. These include syndromes that affect brain structure or make the brain more susceptible to damage. The genetic basis of these auditory processing deficits observed with other developmental disorders remains unclear.
- Neurological conditions such as tumours, stroke and MS.
- Auditory deprivation, e.g. following otitis media with effusion or other type of peripheral hearing loss.
- In the presence of other higher order disorders such as attention deficit disorder, dyslexia, specific language impairment – although in these cases no causal link has been established.
- Age-related changes of the central auditory system, distinct from age-related cochlear hearing loss or cognitive decline.
- Finally, some forms of tinnitus and musical hallucinations, attributed to abnormal activity of the auditory brain may be examples of ‘positive’ disorders of auditory processing.

The following examples illustrate well-recognized presentations of these pathologies. Recent work with insular stroke cases has demonstrated more subtle defects of central processing.

Cortical hearing impairment

Cortical hearing loss is rare, but is most commonly associated with vascular disease or trauma affecting both temporal lobes. Additional and more dramatic neurological sequelae, including hemiparesis and dysphasia, are the rule. The primary auditory cortex lies in the anterior–posterior transverse temporal gyrus of Heschl. Each ear has bilateral representation in the auditory cortex, and thus it is possible to remove the non-dominant hemisphere in humans without significant effect on either the pure-tone audiogram or the discrimination of distorted speech.

In some cases, the primary auditory deficit predominates, and these cases are described as true cortical deafness. In this situation, a patient may present with no subjective experience of hearing, and demonstrate profound hearing loss on pure-tone audiometry. This may be misdiagnosed as peripheral if electro-acoustic and electrophysiological testing are not conducted. For example, oto-acoustic emissions and ABR will demonstrate normal peripheral auditory function. However, abnormal central auditory function will be identified by the later auditory evoked potentials, specifically the middle latency response N1 and P2 waves.

Auditory agnosia

Auditory agnosia was defined originally as a selective disorder of sound recognition: 'I can hear you talking, but I cannot translate it.' This group can be further subdivided into several different clinical presentations: those who are unable to recognize a particular type of sound, e.g. speech, music or particular environmental noises, such as a dog barking, and those who are unable to discriminate at all between verbal and non-verbal sounds. Most cases correspond to the wider definition with impairment of all modalities of auditory function. Nonetheless, there are also cases of verbal auditory agnosia ('word deafness') in which speech perception is severely impaired, while recognition of non-verbal material such as musical tunes embedded within environmental noise remains intact.

Interhemispheric lesions

Patients with surgical section of the posterior corpus callosum demonstrate a typical pattern of auditory processing test results termed the Auditory Disconnection Profile. Characteristically, they have normal performance on monaural low-redundancy speech tests, left ear deficits on dichotic speech tests and bilateral deficits on temporal pattern testing.

Management of auditory disorders

Management of hearing impairment includes:

- Prevention to ensure protection from noise hazards; and avoidance of ototoxic drugs;
- Medical management of systemic medical conditions that may be causing or exacerbating auditory dysfunction; and
- Auditory rehabilitation – a problem-solving exercise centred on each individual patient.
- Hearing aids.

Many cases of cochlear hearing impairment are helped by hearing aids, but additional impairments such as arthritis or cerebellar dysfunction confound the fitting process. Importantly, provision of a hearing aid is only effective when the patient wishes to pursue this line of management, rather than it being the suggestion of well-meaning family members or others. The value of environmental aids and instruction in communication skills also helps long-term rehabilitation.

Hearing aids

Hearing aids have a pivotal role in audiological rehabilitation; precise details of their prescription is outside the scope of this chapter. Conventional aids may be body-worn, head-worn by mounting in spectacles, or mounted in or around the ear. The major advantage of body-worn aids is the very high gain and maximum output achieved, whereas the disadvantage is the obvious and unsightly nature of the device, and the poor microphone placement. Post-aural, in-the-ear or in-the-canal hearing aids are often highly effective, but some patients will require additional environmental aids, e.g. amplification systems attached to TVs or telephones, alerting warning devices, e.g. flashing lights connected to a door bell or an alarm clock.

The need for counselling of hearing-impaired people and their relatives or carers cannot be overemphasized. Simple tactics such as ensuring that light is always on the speaker's face, with the better ear tilted towards the speaker, and minimizing background noise can really help communication. Psychological support should always be considered, and social and occupational support offered.

Conductive hearing loss

Any obstruction to the transmission of sound through the external ear by a foreign body, wax, polyp, tumour or infection must be corrected. Acute otitis externa requires suction clearance under microscopy, culture and sensitivity of the organism, and appropriate medication, with or without steroids. Acute otitis media requires pain relief, re-establishment of Eustachian tube function using nasal drops, inhalations or decongestants, mucolytics and systemic antibiotics: amoxicillin is the usual drug of choice. Vaccines have been introduced against *Streptococcus pneumoniae, Neisseria catarrhalis*, respiratory syncytial virus, adenovirus, influenza A and parainfluenza viruses. Chronic suppurative otitis media requires antibiotics to eliminate infection, followed by surgical repair of a perforated ear drum or damage to the ossicles; this helps prevent reinfection and improve sound transmission.

Conductive hearing loss caused by otosclerosis or hereditary osseous dysplasias may be managed conservatively using hearing aids, or surgically by stapedectomy. The procedure carries a small risk of complication of late sudden sensorineural hearing loss, and for this reason stapedectomy is not generally undertaken on both ears. Congenital malformations of the auditory canal and the middle ear may be treated conservatively with bone conduction or bone-anchored hearing aids or may be surgically remediable.

Sensorineural hearing loss

The management of sudden sensorineural hearing loss is a medical emergency requiring hospital admission, bed rest and investigation of possible causes. In the case of bilateral hearing loss, psychological and aggressive auditory rehabilitation are required. There is no universally evidence-based treatment, and a spontaneous recovery rate of approximately 65% is usual. Proposed therapies include inhalation of carbogen (CO_2–oxygen mixtures), hyperbaric oxygen, antiviral treatment, immunosuppression, calcium-channel blockers, steroids, blood volume expanders and various combinations of these different treatment strategies. Randomized controlled studies have demonstrated the efficacy of systemic steroids, but follow-up has questioned their benefit. Steroid therapy is often contraindicated in the presence of bacterial infection, recent surgery, peptic ulceration, a history of TB, poorly controlled hypertension or diabetes.

The management of progressive hearing impairment depends on the underlying aetiology. Syphilitic labyrinthitis is treated with steroids and penicillin, while rapidly expanding CPA tumours are surgically removed or treated with laser therapy. In the majority of cases of small tumours, however, a ‘watch, wait and monitor’ policy is effective. Immune-mediated sensorineural hearing loss requires urgent management with steroids and/or immunosuppressives following diagnosis. The treatment of Ménière’s disease remains empirical. Therapies can be divided into medical regimes, including dietary modifications, drugs (diuretics, vestibular sedatives, drugs aimed at improving the circulation of the inner ear and immunosuppressives), psychological support, physiotherapy and auditory rehabilitation. A recent low-pressure pulse generator (Meniett device) has been advocated as a non-invasive effective treatment for Ménière’s disease, but there is no definite evidence of efficacy. Conventional surgical treatment is considered when medical management has failed to control vertigo. Chemical labyrinthectomy using intra-tympanic gentamicin has superceded surgical interventions as a method of controlling severe vestibular symptoms, although no clear treatment protocol has been established and cochleo-toxicity is a significant risk. Chronic symptoms of dizziness resulting from vestibular dysfunction and hearing impairment may be treated with auditory and vestibular rehabilitation.

Chronic sensorineural hearing impairment is managed by appropriate treatment of any relevant medical condition and audiological rehabilitation of residual hearing. The selection and fitting of hearing aids is the key element of rehabilitation for the majority of patients with hearing impairment, but in the last two decades implantable devices have revolutionized auditory rehabilitation. Middle ear implants (vibrators on one of the ossicles or on the tympanic membrane) may be used with all types of hearing loss, although their value is not yet clearly defined. Cochlear implants, in one or both ears, are widely used in profound hearing impairment, e.g. congenital loss or secondary to meningitis, superficial siderosis, mitochondrial disease and head trauma. As with all hearing aid provision, the patient requires long-term auditory training within a specialized multidisciplinary team following implantation.

VIIIth nerve disorders

Patients whose test results fulfil the criteria for auditory neuropathy represent a heterogeneous group in whom degraded speech perception inconsistent with pure tone sensitivity remains the common feature. Management strategies will be determined by the age of the patient.

Amplification and rehabilitation strategies

Early language intervention

For children with auditory neural dyssynchrony (AN), the onsets of plosive consonants and transitions – which make speech intelligible – are lost, preventing these children from categorizing or sequencing sounds. A phoneme-based language therapy known as cued speech is used. This is a method whereby cues to vowel and consonant sounds that are difficult to perceive from lip-reading, can be given by synchronous hand-shapes presented alongside either the mouth or pharynx of the speaker. These cues will give syntax and phonological structure to language and are more easily learned by parents.

Hearing aids

Various studies have examined the benefits of hearing aids, and shown variable results. The main concern regarding the use of hearing aids in patients with AN is that they can cause significant noise exposure and permanent threshold shift (up to as much as 20 dBHL). The use of an algorithmic approach to hearing aid fitting and real ear measures to verify parameters of the hearing aid needs to be calculated in much the same way as for the risk–benefit analysis for children with sensorineural hearing loss.

Gap detection and modulation transfer function are abnormal in AN patients, and a speech-processing type of hearing aid with a high-frequency emphasis to enhance high-frequency transient speech sounds, i.e. consonants, has been recommended. Also the use of directional microphones and personal FM systems to improve the signal : noise ratio in those patients with pronounced difficulties with speech in background noise has been proposed.

Use of cochlear implants

Studies are now being published as to the benefit of cochlear implantation (CI). Studies report small numbers only in children, all of whom had undergone a trial period of powerful behind-the-ear aid use. Neural response telemetry (NRT) is used to assess neural synchrony and temporal coding post-cochlear implant. The presence of the electrically evoked compound action potential (ECAP) is interpreted as indicating that electrical stimulation has restored some degree of synchrony and temporal encoding at the level of the cochlear nerve. Generally, authors conclude that

CI should be performed only after a trial of conventional amplification and that each decision to implant must be based on the individual circumstances. Auditory brainstem implants have been used in profoundly deaf patients in whom there is complete dysfunction of the VIIIth nerve, e.g. in NF2.

Auditory processing disorders

Intervention for APD is multidisciplinary. Test results help to determine appropriate strategies for each patient. Intervention strategies include environmental modifications, signal enhancement, speaker adaptations, auditory training and compensatory strategies. While there is some evidence to suggest that these manoeuvres help, there are no robust trials to support them. Management is currently based on clinical judgement, and there is much individual variation between units. APD is an expanding field, and there is need for systematic, validated tests, and for studies to assess efficacy of interventions.

Environmental modifications

Noise and sound reflections from surfaces within a room distort and degrade acoustic signals. A noise survey of the acoustic environment, e.g. the classroom, may help determine first whether it adheres to UK building regulations that define the upper limit of noise and, secondly, identify potential corrective measures, such as carpets, curtains, acoustic panelling and sealing of doors and windows.

Signal enhancement strategies

Personal or soundfield FM systems are devices that receive and amplify speech, via a microphone/transmitter, both worn by the speaker. The amplified signal is then transmitted via FM wireless waves to loudspeakers (soundfield) or a special receiver (personal system) that the listener wears in or over the ears. These systems help counteract background noise, sound reflections and loss of acoustic energy over distance.

Relatives and carers: speaker-based adaptations

Speakers, i.e. those in contact with the patient, should be taught how to deliver speech at a slightly slower pace than normal, segment speech and stress different speech segments in order to enhance a message. In addition, rephrasing rather than repetition, and use of visual or other cues may be of help.

Auditory training programmes and compensatory strategies

Auditory training can help in both auditory and non-auditory performance, such as language and reading, and may actually modify cortical neural representation. Informal auditory training does not require technical resources; activities are chosen from the patient's complaints and test results. Patients can perform these programmes unaided or with help of a therapist. Auditory training tasks can be in computer game format, with adaptive procedures, i.e. tasks become more difficult as the listener improves. Examples of computer-based auditory programmes include:

- Earobics (http://www.earobics.com/);
- FastForWord (http://www.scilearn.com/);
- Phonomena (http://www.mindweavers.co.uk); and
- Brain Fitness for older adults (http://www.positscience.com).

The Brain Fitness programme consists of six adaptive exercises that aim to enhance fidelity in auditory sensory input and language representations during hour-long sessions, 5 days/week over 8 weeks. One study of patients >60 years showed that those who completed the programme improved significantly in trained tasks and in auditory memory and that improvement was maintained for 3 months. Compensatory strategies include active listening, auditory vigilance training, auditory memory enhancement, metacognitive, linguistic, metalinguistic and other strategies.

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15 Spinal Cord Disorders

Simon Farmer, Adrian Casey, David Choi, Robin Howard, Geoffrey Raisman

Clinicians involved in the diagnosis and management of spinal disease face formidable challenges. While advances in neuroimaging have provided great insight into the disordered anatomy that underlies many conditions there is still much to be learnt about the basic mechanisms of disordered development, the physiology and pathophysiology of spinal cord function, the mechanisms of spinal repair and effective rehabilitation, neuro-inflammation and infection. Spinal surgery from the neurosurgical and orthopaedic perspectives is a rapidly developing field. Spinal disease is a multi-disciplinary subject with important contributions from neurologists, neurosurgeons, orthopaedic surgeons, rheumatologists, neuroradiologists, neurophysiologists, pain specialists, rehabilitationists and the multidisciplinary team. This chapter discusses spinal embryology and anatomy, spinal physiology, clinical assessment of spinal cord disease, congenital malformations of the spine, spinal trauma and strategies for spinal repair, spinal compression and tumours, degenerative spinal disease, spinal inflammation and infection, vascular disorders of the spine and conditions including arachnoiditis and siderosis in which the spine is dominantly involved.

Embryology of the spine

The adult spine is divided anatomically into the cranio-cervical junction, and the cervical, thoracic, lumbar and sacro-coccygeal spine. Developmental abnormalities may arise at each level. Interpretation of congenital and acquired anomalies of the vertebral column is aided by an understanding of normal development. In early fetal life the ectodermal germ layer gives rise to the primitive neural tube which, in turn, gives rise to the entire nervous system during primary neurulation. This normally closes by the end of the fourth intrauterine week; failure of this primary neurulation results in fusion defects such as anencephaly or spina bifida. By this time the primary brain vesicles are present, representing forebrain, midbrain and hindbrain. Mesoderm lies around the neural tube and by the end of the fifth intrauterine week will have completed segmentation into recognizable somite pairs (occipital to coccygeal). Once established, the epithelioid cells of these somites rapidly transform and migrate towards the notochord where they differentiate into three distinct cell lines: sclerotomes (from which connective tissue, cartilage and bone are derived), myotomes (providing segmental muscle) and dermatomes (providing segmental skin). Chondrification of the sclerotomes leads to the development of ossification centres, with an anterior and posterior centre for each vertebral body and a pair for each arch. The process is largely complete by the end of the third month of fetal development.

Disruption during these early stages accounts for many of the vertebral and cranio-cervical anomalies. After the third month of gestation the vertebral column and dura lengthen more rapidly than the spinal cord resulting in regression of the cord tip, leaving the filum terminale below. By term, the cord tip typically lies at the L2–3 interspace. Secondary neurulation arises in the distal sacral and coccygeal segments and does not produce functioning neural elements. Problems with secondary neurulation may give rise to lipomas of the filum terminale and tethering which prevents the normal ascent of the spinal cord during vertebral growth. Therefore, the conus medullaris continues to lie below its normal position at the L1–2 border.

The fetal spine can be reliably identified on ultrasound at 12 weeks and an accurate assessment of its integrity can be determined by 20 weeks.

Genetic control of spinal development

The notochord provides the template for spinal development although only remnants of it persist in the nucleus pulposus of the cartilaginous discs. The notochord orchestrates the production of numerous signalling molecules between it and the neural

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Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

tube and somites, initiated by the production of the protein product of a notochord gene called 'Sonic Hedgehog'. Sonic Hedgehog induces differentiation in the ventral and lateral neural tube as well as sclerotome differentiation in the somites. Mesoderm around the neural tube segments into 44 somite pairs (4 occipital, 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 10 coccygeal) by the end of the fifth week. The segmentation process itself is complex. In the chick, mouse and human embryo segments are formed sequentially. The driver for presomitic mesoderm segmentation may involve an intrinsic molecular oscillator 'the segmentation clock'. There is rhythmic production of mRNA from several genes related to the Notch gene-signalling pathway. In chick embryos the periodicity is approximately 90 minutes with new somites being formed sequentially. The Notch-related genes include *Lunatic Fringe*, *Delta* and *Presenilin 1* (see figure 15.1 from Giampietro *et al*. 2003). Failure of oscillatory signalling may lead to failure of segmentation in a rostral–caudal direction where the first most caudal somites (whose ultimate fate is to be at vertebral level) are formed normally but then there is progressive loss of segmentation because of degradation of the molecular rhythmicity leading to anomalies of the most rostral vertebra.

While the Notch genes specify longitudinal segmentation of the developing spinal cord, another group of genes, the *Hox* (homeobox) family, specifies axial development. In humans there are four families of *Hox* genes which are also expressed from caudally to rostrally, but with differing rostral extents. A rostrocaudal signal is therefore created in the developing embryo, which specifies positional values to each spinal level. Abnormal expression can be demonstrated in transgenic mice, e.g. mutation of *Hox-b4* results in duplication of the atlas, such that a second atlas replaces the axis vertebra.

Identifying genetic mutations involved in spinal anomaly

Much of the research effort into understanding the genetics of spinal developmental anomaly involves the study of conservation of genes during evolution (possibly only 200 chromosomal rearrangements in total since the mouse and human lineages diverged), which means that detailed study of the mouse genome may yield important homologues of human genetically determined spinal maldevelopment. Syntegy conservation may be used to identify fruitful areas of the mouse and human genome in which mutations may produce phenotypes recognizable in human developmental disorders. This allows the search for causative genetic mutations in human malformations to be narrowed. From analysis of mouse developmental abnormalities and comparison to homologous human malformations which include spinal malformation, the following genes have been identified: *Hox*, *Notch*, *Pax1*, *Mox1*, *Gli*, *Unex4.1*, *BMP-7* and *Jun*. Mutations in the *Pax1* gene have been associated with vertebral anomalies in humans.

A new technique of Cre-recombinase-mediated transgenesis mapping has been used to map the destinations of embyronic neural crest and mesodermal stem cells. This mapping has been resolved at the single cell level and it reveals that the boundaries traverse homogeneous skeleton of neck and shoulders. From this mapping it has been discovered that in vertebrates the neural crest anchors the head to the anterior shoulder girdle. Mesoderm, which is controlled by expression of a *Hox* gene, links trunk muscles to the posterior neck and shoulder skeleton. It has been suggested that muscle attachments may be a new way of defining homologous pieces of skeleton. The skeleton identified using the Cre-recombinase technique is abnormal in Klippel–Feil and Chiari malformations. This genetic mapping technique may greatly increase our understanding of head, neck and shoulder morphology; furthermore, it situates human, head, neck and shoulder anomalies in a context that reflects the known complexity of neck and shoulder evolution in vertebrate lineages.

Human vertebral segmentation defects

Numerous congenital defects of the spinal column have been identified that result from segmental disruption. These include Klippel–Feil syndrome, Alagille syndrome, spondylocostal dysostosis (Jarcho–Levin syndrome), congenital scoliosis and kyphosis, Goldenhar syndrome and the VATER (vertebro-anal-tracheo-esophageal-renal) and VACTERL (vertebral-anal-cardiac-tracheo-esophageal-renal-limb) syndromes. In many of these syndromes there are severe abnormalities affecting a number of body parts. The vertebral segmentation abnormalities may be generalized, regionalized or localized. The vertebral abnormalities (including wedge, hemi- or butterfly vertebrae) that give rise to congenital scoliosis and kyphosis are likely to involve problems of somitogenesis. Two mutations in the Notch signalling pathway have been identified these are *Delta-like 3* in spondylocostal dysostosis and *Jag1* in Alagille syndrome. Spondylocostal dysostosis is dominantly and recessively inherited with multiple segmentation abnormalities of vertebra, axial skeleton and ribs leading to a non-progressive kyphoscoliosis. Alagille syndrome is a severe multi-organ disorder affecting the liver, heart, eyes, facial bones associated with vertebral segmentation defects. It is likely that Klippel–Feil syndrome results from a disorder either in *Notch* gene signalling or the *PAX* gene but as yet the genetic aetiology is unknown. Furthermore, the syndrome may also be caused by non-genetic errors of development, e.g. resulting from teratogens, and the long narrow shape of the unsegmented vertebral bodies might suggest a problem around the time of chondrification.

Split-cord malformations may occur during development, either anteriorly resulting from a split notochord, or posteriorly because of incomplete closure of the neural tube. A split notochord is likely to induce the development of split vertebral bodies, separated by invaginating gut endoderm or an accessory neuroenteric canal.

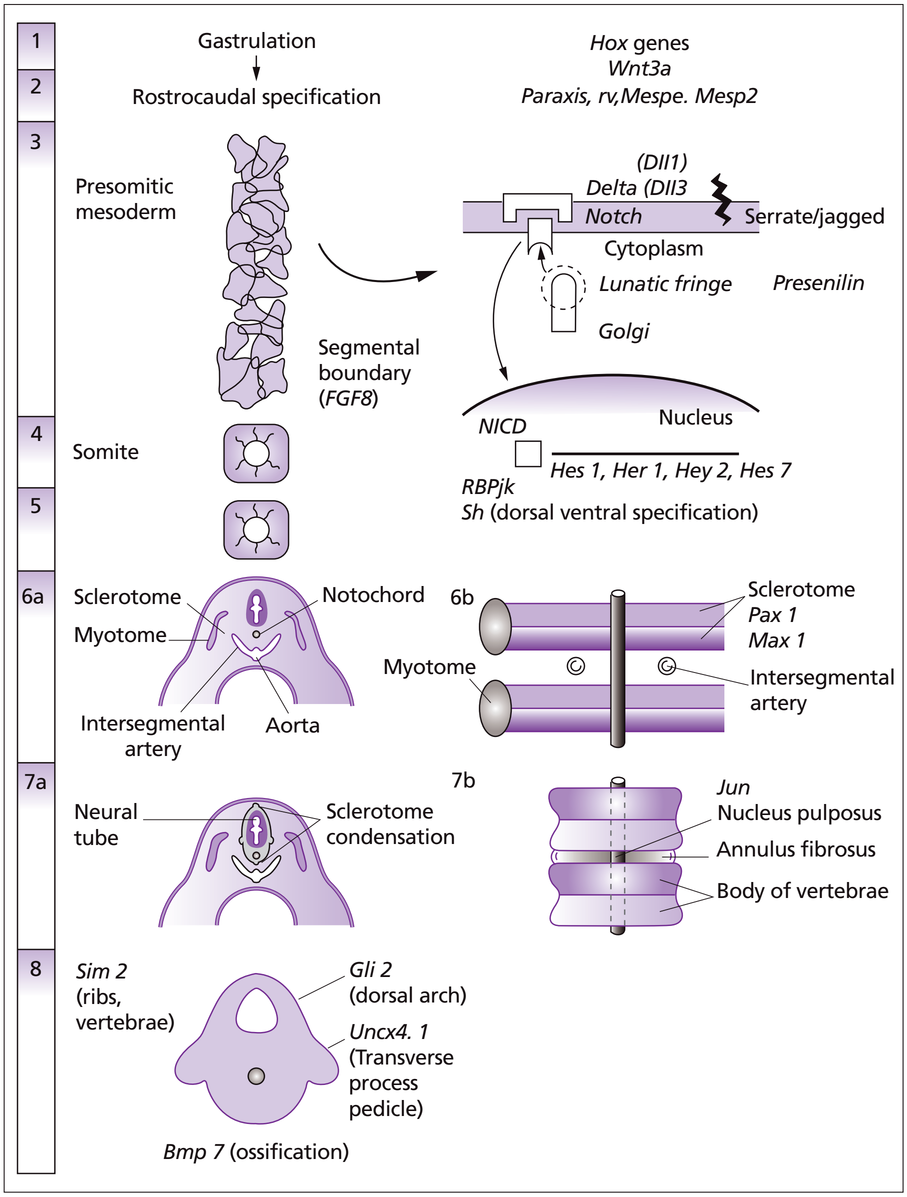

1
2
3
4
5
6a
7a
8
Gastrulation
Rostrocaudal specification
Hox genes
Wnt3a
Paraxis, rv,Mespe. Mesp2
Presomitic mesoderm
(Dll1)
Delta (Dll3
Notch
Serrate/jagged
Cytoplasm
Lunatic fringe
Presenilin
Golgi
Segmental boundary (FGF8)
NICD
Nucleus
Hes 1, Her 1, Hey 2, Hes 7
RBPjk
Sh (dorsal ventral specification)
Somite
Sclerotome
Myotome
Notochord
Intersegmental artery
Aorta
6b
Sclerotome
Pax 1
Max 1
Myotome
Intersegmental artery
Neural tube
Sclerotome condensation
7b
Jun
Nucleus pulposus
Annulus fibrosus
Body of vertebrae
Sim 2 (ribs, vertebrae)
Gli 2 (dorsal arch)
Uncx4. 1 (Transverse process pedicle)
Bmp 7 (ossification)

Figure 15.1 Possible steps in mouse spinal development with relevant genes (in text).

Abnormalities of the atlas and axis vertebrae probably also occur because of intrauterine trauma rather than abnormalities of genetic expression. Anterior and posterior spina bifida of the atlas occur in mucopolysaccharidoses and Down's syndrome where excessive movement at the stage of chondrification of the atlas probably results in an incomplete bony ring.

Clinical assessment of spinal disease

In this section the primary focus is on those symptoms and physical signs that are of particular value in helping the experienced clinician achieve an accurate and timely diagnosis and an assessment that allows a coherent plan of management to be formulated.

Cranio-cervical junction

Symptoms and signs may be insidious or rapid in onset. Clinical presentation is diverse depending on the level affected.

The lower brainstem, cranial nerves, cervical roots and upper cervical cord may be compromised by pressure from bone or soft tissue, there also may be indirect compromise of the blood supply. Congenital anomalies of the cranio-cervical junction are often associated with dysmorphic features and obvious skeletal anomalies. Patients most commonly complain of headache and neck pain worsened by movement and coughing. Pain characteristically originates in the suboccipital region and radiates to the vertex in a C2 distribution. Head tilt and torticollis are more common in children, but may sometimes occur in adults. In children with cranio-cervical junction anomalies, hearing loss is the most common cranial nerve symptom. In adults, trigeminal distribution pain and neuralgia may result from direct compression of the Vth nerve or compression of the Vth nerve nuclei in the upper cervical cord. Lesions of other cranial nerves, particularly IX, X, XI and XII, are also seen. Spinal cord compression produces a myelopathic picture with upper motor neurone features, which may progress to involve bladder and bowel control. Occasionally, the myelopathy is confined to the upper limbs. There may be a predilection for the dorsal columns, producing marked joint position sense loss. Brainstem involvement may produce dysphagia, dysarthria, internuclear ophthalmoplegia and nystagmus (most commonly horizontal but more classically down-beating). Central apnoea, vivid nightmares associated with sleep apnoea, drop attacks and syncope are important additional features. The intimate relationship of the vertebral arteries to the upper cervical spine and foramen magnum may increase the risk of vertebro-basilar ischaemia. Sequential 'clock-face' involvement of limbs may occur with neural compression at the foramen magnum: spastic weakness of the extremities with progression of motor symptoms, which may begin in the ipsilateral upper limb, followed by weakness of the contralateral lower limb and progressing to the contralateral upper limb, caused by compression of the pyramidal decussations. 'Cruciate paralysis' and dissociated sensory loss are often associated with pressure on the upper portion of the pyramidal tracts and an intramedullary process, respectively.

Syringobulbia and syringomyelia

Cavitation of the spinal cord sometimes extending into the brainstem is an association of cranio-cervical junction anomalies. The symptoms and physical signs reflect a pathology that starts centrally and expands outwards. The patient complains of painless injuries, muscle wasting and weakness and more rarely limb weakness. More unusual presentations, e.g. central apnoea, also occur. The classic onion skin sensory loss of syringobulbia is caused by involvement of the spinal nucleus or the tract of the trigeminal nerve and may be associated with tongue wasting, trigeminal pain, palatal and laryngeal weakness and symptoms of medullary involvement. The cavity in syringomyelia affects crossing spinothalamic fibres producing a half-cape or cape loss of pain and temperature sensation; posterior column signs are also found. There is amyotrophy at the level of the cavity with tendon reflex loss. In advanced stages Charcot joints develop. Below the cavity there may be upper motor neurone symptoms and signs and disturbances of sphincter function, which contrast with the lower motor neurone symptoms and signs at the level of the syrinx.

Cervical spine

The presenting symptoms of cervical spine disease reflect the aetiology. As degenerative disease is the most common condition affecting the cervical spine, pain is the most frequent presenting symptom. The nature and distribution of the pain is a useful pointer to the site and nature of the pathology. In spondylotic disease, typically there is a dull ache in the neck worsened by movement. Spurling's sign is a reliable test of mechanical root compression (axial loading of the head, with simultaneous lateral flexion and rotation of the neck). The radicular component of the pain is often a dull ache with sharper exacerbations. Cough impulse pain may frequently accompany disc protrusion or prolapse. The symptoms and signs of weakness and numbness may localize a particular radicular level, but the spinal level of traditional dermatomes and myotomes may vary by a level up or down. Below the pathological level there may be upper motor neurone symptoms, signs and a spinal sensory level reflecting cord compression. The patient's complaints can often suggest cervical instability: 'My head feels loose' or 'I have to hold my head' and should not be discounted as an anxiety disorder. Lhermitte symptoms resulting from posterior column compressions may also occur as a result of cervical instability. Hand weakness in high cervical cord compression may be caused by a combination of pyramidal tract compression and de-afferentation from dorsal column involvement. It can be difficult to describe by a patient. When asked to explain their symptoms, there is often a characteristic pause, the patient looks at their hands while opening and closing them in a slow, poorly coordinated fashion, while trying to articulate what is wrong: 'They just don't work. . . . I just can't do anything with them'.

Thoracic spine

Degenerative thoracic spine disease typically presents with local or radicular pain but few other symptoms or signs until spinal cord compromise develops, at which point there is usually a combination of upper motor neurone weakness, a spinal sensory level and sphincter disturbance. Thoracic arteriovenous malformations (AVMs) and fistulas may initially present with chronic subtle or intermittent symptoms which progress with time.

Lumbar and sacrococcygeal spine

Degenerative disease is the most common pathology at this site, therefore pain, which may be localized and radicular, is the most common presenting complaint. This pain is usually a dull ache with exacerbations which is often movement sensitive. The anatomical distribution of the radicular component of the pain and the physical signs demonstrate the site of the pathology. In nerve root lesions lower motor neurone signs reflect the myotomes innervated by the root. For example, wasting of extensor digitorum brevis over the dorsum of the foot indicates an L5 innervated muscle. Tendon reflex loss is a further important indicator of the nerve roots involvement. Sensory loss reflects the dermatomal distribution of the affected root.

Degenerative lumbar canal stenosis presents with low back pain, leg pain, heaviness or weakness often worsened by exercise and standing straight. Patients with so-called spinal claudication prefer to adopt a slightly flexed posture and may find it easier to walk leaning on a shopping trolley, or frequently squat down as if to tie a shoelace. They may be able to ride a bicycle for a longer period of time than they can walk, again because of the flexed riding position. Leg weakness and tendon reflex loss may be exercise-dependent and therefore patients should be examined after they have walked. These findings are important in distinguishing spinal claudication from vascular claudication, which is worse with increased muscular activity, affecting more often the calf muscles, does not vary with posture and is associated with trophic skin changes. Cauda equina pathology may also present insidiously and the clinician needs to be alert for sphincteric involvement, disturbances of sexual function and saddle sensory loss.

Other clinical features of spinal disease

It is important to examine for spinal deformity especially scoliosis and kyphosis. If a spinal deformity is evident then the examination should, as well as seeking evidence for local spinal disease, also consider generalized neuromuscular conditions and neurocutaneous conditions. Neurofibromatosis Type 1 in particular may be readily diagnosed by the presence of café-au-lait spots, shagreen patches, Lisch nodules, axillary freckling and cutaneous neurofibromas. Papilloedema is an uncommon but recognized sign of spinal pathology and is associated with high cerebrospinal fluid (CSF) protein. Autonomic symptoms and signs are of limited localizing value but are seen in severe spinal lesions in which there is loss of temperature control and disturbances of sweating.

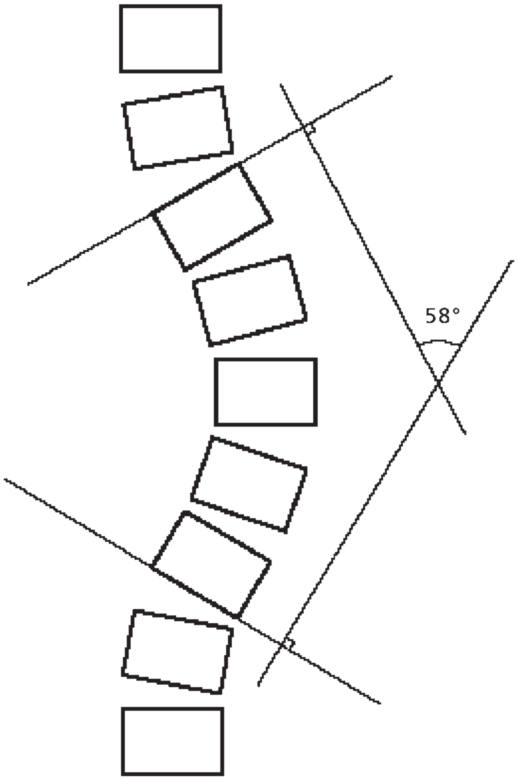


Figure 15.2 Cobb angle. Diagram illustrating method of calculating the Cobb angle to guide treatment of scoliosis.

Spinal deformity

Idiopathic scoliosis

Scoliosis refers to a lateral deviation of the spine in the coronal plane and is always abnormal. It may be classified on the basis of clinical examination into structural and non-structural forms. In a structural scoliosis there is a rotational component to the curve, which is best seen on forward flexion when prominence of rib or loin musculature becomes apparent. This is not the case in non-structural scoliosis, where there is no rotational element. Non-structural scoliosis may be a marker of other pathology such as leg length discrepancy or muscle spasm but is rarely of clinical significance in itself. However, if associated with underlying neurological disease it may progress to a structural deformity.

Once a structural scoliosis is diagnosed, the severity and potential for progression must be assessed. Erect posterior–anterior and lateral X-rays should be taken in a standardized manner so that serial films can be compared. The severity of the curve is given by the Cobb angle, which describes the angle created by the intersection of lines drawn across the end-plates of the upper and lowermost vertebrae delineating the curve, i.e those with the greatest opposing tilt as illustrated in Figure 15.2. Angles >20° in skeletally immature children demand particular vigilance for it is during periods of rapid growth that scoliosis may progress significantly. Scoliosis presenting in younger children thus has a greater risk of progression. Progression of scoliosis in adults is less common, although underlying neuromuscular disease, pregnancy and osteoporosis pose increased risks. In general, 25% of scolioses do not progress, 25% progress slowly and 25% progress rapidly.

The major causes of structural scoliosis are given in Table 15.1. The most common type is idiopathic scoliosis accounting for around 70% of all cases. The child is otherwise healthy and no underlying pathology is found. The prevalence of adolescent scoliosis, the most common form, is approximately 4% of the population if mild cases are included. The majority of idiopathic scoliosis are right-sided, thoracic and painless.

The cause of idiopathic scoliosis is multi-factorial and the development and progression of the scoliosis may have different mechanisms. There is often a positive family history of scoliosis, with girls eight times more likely than boys to require treatment. The pattern of inheritance is consistent with a dominant major gene diallele model (the gene is as yet unidentified) with incomplete penetrance. Progression of the curve is more common in thoracic or large curves (>35°) with skeletal maturity another important consideration. The consequences of severe idiopathic scoliosis are cosmetic deformity, cardiopulmonary compromise and back pain.

Table 15.1 Causes of structural scoliosis.

Idiopathic scoliosis
Infantile <3 years
Juvenile 3–10 years
Adolescent >10 years

Congenital scoliosis
Failure of vertebral segmentation and/or formation

Neuromuscular scoliosis
Neuropathic
Upper motor neurone
- Cerebral palsy

Lower motor neurone
- Spinal muscular atrophy, poliomyelitis, hereditary neuropathies and dysautonomias

Mixed
- Myelomeningocoele, spinal dysraphism, tethered cord, syrinx

Myopathic
- Congential myopathies
- Muscular dystrophies, e.g. Duchenne

Miscellaneous causes
Skeletal dysplasias
Marfan's syndrome
Neurofibromatosis
Spinocerebellar degenerations including Friedreich ataxia
Arthrogryposis
Rett syndrome
Metabolic bone disease
Dystonia
Parkinson's disease and parkinsonian syndromes
Cranio-cervical junction anomalies especially if associated with syringomyelia
Spinal tumours/trauma/irradiation

Congenital scoliosis

In congenital scoliosis the vertebrae are anomalous either because of a failure of natural segmentation, leading to asymmetric fusion, or to failure of formation, in which only part of the vertebra is formed (see discussion above on processes of segmentation/vertebra formation). Often there is a combination of both pathologies. Failure of segmentation may lead to a unilateral fused bar with scoliosis away from the fused side, or a block vertebra. Abnormalities in mesenchymal formation may lead to mild wedging or absence of half a vertebra producing a hemivertebra with a single pedicle and lamina with subsequent scoliosis. In congenital scoliosis there is a high incidence of associated anomalies. These include neuraxis anomalies in up to 40% of patients, renal and gastrointestinal tract abnormalities in 20% and congenital heart defects in approximately 10%. Sometimes the scoliosis is part of a syndromic diagnosis such as in the Klippel–Feil and Noonan syndromes. Clinically the scoliosis may vary from a mild non-progressive deformity to a severe and rapidly progressive curve that compromises the spinal cord.

Neuromuscular scoliosis

Spinal deformity is common in many of the neuromuscular disorders. In the developed world cerebral palsy, spina bifida and Duchenne muscular dystrophy are the most common causes of neuromuscular scoliosis, although poliomyelitis is still an important cause in developing countries. Because of the underlying condition, the spinal curvature, in contrast to idiopathic scoliosis, generally presents earlier, is more extensive and is more likely to deteriorate through childhood and into adult life. Other systems are often already compromised, e.g. there may be muscle imbalance, cardiopulmonary insufficiency, poor nutrition, insensate skin and osteoporosis. The physical and functional effects of the scoliosis often exacerbate these problems. In addition, the scoliosis may adversely affect walking and seating and cause pain as the ribs abut the iliac crest. This is often compounded by coexisting pelvic obliquity, particularly in the non-ambulant patient.

Kyphosis and lordosis

The spine naturally shows some curvature in the anteroposterior plane, seen as a kyphosis in the thoracic region and lordosis at the lumbar spine. A normal lumbar lordosis shows full correction on forward flexion. A kyphosis >40° is abnormal. It may be congenital, caused by a lack of fusion of the vertebral bodies anteriorly or a lack of formation of one or more anterior bodies. Although less common than congenital scoliosis it carries a more severe prognosis, as a higher proportion of patients will develop progressive deformity and myelopathy, particularly during the adolescent growth spurt. Patients with anterior failure of vertebral body formation who present with a sharp angle kyphosis are at particular risk of rapid progression and spinal cord compression. Early arthrodesis is indicated in these cases. Other causes of abnormal kyphosis include Schuermann kyphosis, post-trauma, osteomalacia, osteoporosis and tumour infiltration. Schuermann kyphosis is the most common form of acquired kyphosis. Presenting in adolescents, it is generally benign and may be corrected with a brace if applied during the adolescent growth spurt. Kyphosis only occasionally progresses once skeletal maturity is reached.

Miscellaneous causes of spinal deformity

A number of primary diseases of bone and connective tissue produce pathology of the spine and cranio-cervical junction. Those that present neurological problems are classified into four broad categories.

Osteopenic disorders

In osteopenic disorders bone mineralization is reduced. These include endocrine diseases such as hyperparathyroidism, Cushing disease, osteomalacia, primary osteoporosis and osteogensis imperfecta.

Osteogenesis imperfecta (OI) is a heritable disorder of collagen that results in osteopenia and increased bone fragility. In 95% of patients mutations are found in the genes (*COLIA1* and *COLIA2*) encoding the $\alpha1$ and $\alpha2$ collagen chains. This results in reduced amounts of collagen which is often structurally abnormal. To date, over 200 mutations have been found; however, there is no close correlation between the molecular abnormalities and the clinical manifestations which are highly variable.

Prenatal diagnosis is available for some forms of the disease. The Sillence classification delineates four major phenotypes on the basis of bone fragility, growth and the presence or absence of additional features such as blue sclerae, dentinogenesis imperfecta and presenile hearing loss. Progressive skeletal deformity is a particular feature of OI Type III and often requires orthopaedic intervention. Basilar invagination is a rare but important complication of OI. This may be associated with ventral brainstem compression, hydromyelia and hydrocephalus. It generally presents in early adult life with progressive neurological symptoms and signs, the most common being headache and lower cranial nerve dysfunction, particularly atypical trigeminal neuralgia. Other features include quadriparesis, ataxia and nystagmus. Trigeminal pain, if intractable, may require stereotactic surgery. The treatment of myelopathy involves ventral decompression and occipito-cervical fusion, with or without decompression of the foramen magnum.

Currently, there is much interest in the role of bisphosphonates in the management of OI. There is evidence that these drugs reduce bone pain, improve both bone density and vertebral height, and improve mobility. However, long-term benefits on disease progression, function and quality of life have yet to be fully demonstrated and there are concerns about long-term adverse consequences of the treatment. Biphosphonate treatment of mild OI is probably not indicated because of the potential long-term risks of therapy.

Skeletal dysplasias

The two largest categories of these disease are the osteochondrodysplasias and the dysostosis. Osteochondrodysplasias are defined as abnormalities of cartilage or bone growth and development. They generally present as short-limbed dwarfism, with autosomal dominant achondroplasia resulting from mutations in the *FCFR3* gene the most common form. Around 50% of children with achondroplasia have a thoracolumbar kyphosis in infancy and there is a risk of spinal cord stenosis. Patients characteristically have macrocephaly but a small mid face and small foramen magnum. These abnormalities place them at risk of symptomatic stenosis and hydrocephalus. Sleep apnoea is seen in the majority of patients, which may have a central or respiratory cause. Cervico-medullary decompression with resection of the foramen magnum may be necessary. Atlanto-axial instability has been increasingly recognized in the skeletal dysplasias.

The dysostosis are defined as malformations of individual bones singly or in combination. These include the craniosynostoses (Crouzon and Apert syndromes) in which vertebral anomalies are commonly recognized and Klippel–Feil syndrome (see below).

Metabolic storage disorders

These include the mucopolysaccharidoses, the glycoprotein storage disorders, the gangliosidoses and the mucolipidoses. These neurodegenerative diseases vary in their severity but show characteristic skeletal dysplasias, such as 'hooked' vertebrae, broad ribs and flared pelvis. Thoracolumbar kyphosis is common, with a risk of spinal cord compression. Other neurological complications include cognitive deterioration, carpal tunnel syndrome and deafness. In Morquio syndrome (mucopolysaccharidosis IV) the os odontium is dysplastic or absent. These patients also have striking ligamentous laxity which gives a particularly high risk of atlanto-axial instablity and spinal cord compression.

Mesenchymal and connective tissue disorders

Around 30% of patients with neurofibromatosis will develop scoliosis, of which 40% will have associated cervical spine abnormalities. The scoliosis often manifests as an acute angled, short segment kyphoscoliosis, which will inevitably progress unless fusion is performed. Approximately 50% of patients with Marfan's syndrome develop significant scoliosis.

Management of spinal deformity

Patient management varies from case to case and will be influenced by the underlying diagnosis, current levels of function, especially ambulatory abilities, life expectancy and concomitant medical problems. In broad terms, surgery may be performed for progressive deformity, neurological symptoms or pain, but is associated with risks, including infection (2–5%) and neurological damage (1–2%). The primary goal of corrective surgery is to produce a balanced spine in the coronal and sagittal planes when non-operative measures have been unsuccessful. However, it should be remembered that a deformity in one part of the spine will often be coupled with a compensatory scoliosis or kyphosis in another, and correction of the primary deformity should be performed in the context of the overall balance of the spine. A lumbar scoliosis, for example, should not be corrected in isolation if it would lead to overall coronal imbalance as a result of persisting 'compensatory' scoliosis elsewhere.

Kyphosis

In kyphosis, bracing is advocated for skeletally immature patients with progressive curves less than 60° (normal range 25–40°). Surgery is often required if the curve exceeds 60°. Correction of a kyphosis should be performed at the lowest level possible to minimize risk, and the presence of any fixed flexion deformity at the hips should be noted and corrected first, because this will affect the overall sagittal balance of the spine.

Idiopathic scoliosis

In adolescents with suspected idiopathic scoliosis, standing lateral and posterior–anterior X-rays should be performed and those patients with curves greater than 20° should be followed by repeat X-rays every 4–6 months. Curves progressing more than 5° in 4–6 months, or exceeding 30°, should be treated with a brace which may delay or arrest scoliosis progression in the skeletally immature child. A thoracolumbar spinal orthosis is generally used, with an added cervical extension (as in the Milwaukee brace) if the apex of the curve is above T8. Bracing is rarely effective once the curve exceeds 45° and it is in these patients that surgery is recommended. Surgery may also be advised if there is a significant thoracic lordosis or rotational deformity that impairs pulmonary function.

Congenital or myopathic scoliosis

In congenital or neuromuscular scoliosis there may be a role for bracing but, given the relentless progression of the scoliosis in many of these conditions, early surgery is often indicated. In non-ambulant patients the spinal fusion should involve the pelvis. Surgical risk, particularly of haemostasis and postoperative chest infection, is high in this patient group.

Neuropathic scoliosis

Neuropathic scoliosis is often associated with rapidly progressing curves in juveniles (3–10-year-olds) with pain and neurological findings that reflect the underlying disease, such as a tethered cord, diastematomyelia or lipoma. It is important to look for signs of a skin dimple, sinus, haemangioma or hairy patch in all children with a scoliosis, and to perform magnetic resonance imaging. Early treatment of the underlying disorder can arrest the progression of the scoliosis, but if treatment is delayed then the curve may reach the point where altered biomechanical forces take effect and the curve continues to progress despite treatment.

If a neurogenic cause for scoliosis is overlooked and the curve is incorrectly believed to be idiopathic, then neurological damage may occur during surgical correction. For example, a tethered cord may be stretched further during instrumentation and straightening of the spine.

Degenerative scoliosis

In adults, scoliosis may occur in later years because of asymmetric degeneration in discs, facet joints or osteoporotic wedging of vertebral bodies. Surgical fixation might be considered in the presence of pain or progressive deformity.

Surgical correction of spinal deformity

Good results are dependent on meticulous patient selection at all stages, with multi-disciplinary pre-operative assessment, experienced specialized spinal surgeons, intraoperative neurophysiological spinal cord monitoring and intensive care support postoperatively. Complications in the immediate peri-operative period include haemorrhage, respiratory and cardiovascular problems. Infection occurs in 2–5% of patients. Paraplegia occurs in 1% of patients and nerve root damage in 1–2%. Up to 5% of patients experience failure of fusion.

In the past, Harrington rods were used to correct deformity by a posterior approach to the spine: these are steel rods with laminar hooks used to open out the concave side of the scoliosis. This technique of unilateral distraction was useful in correcting coronal balance, but not kyphotic deformity. Now the most common surgical technique for correction of deformity is the insertion of pedicle screws, which can be manipulated to good alignment and secured to titanium rods, supplemented with sublaminar and transverse process hooks if required (Figure 15.3). These newer systems of instrumentation allow simultaneous correction of imbalances in the sagittal, coronal and axial planes. Iliac crest bone graft is placed over the construct and between transverse processes to produce a solid fusion.

Standing posterior–anterior and lateral X-rays are required for surgical planning, and primary curves may be identified. Specific

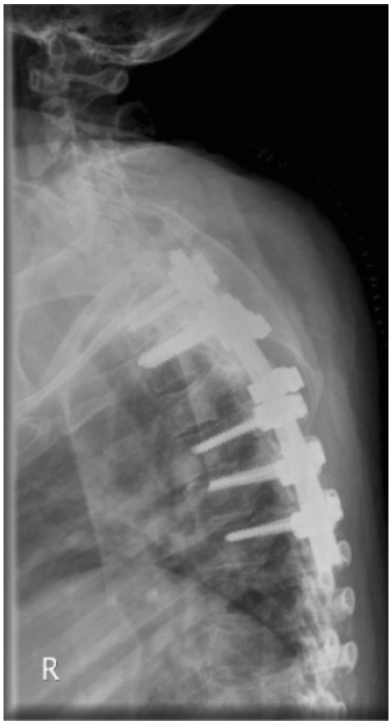


Figure 15.3 Lateral spine X-ray showing pedicle screw fixation for correction of spinal deformity resulting from tumour.

categories of primary deformities and compensatory curves have been described. The endpoints for the fusion and the positions of the pedicle screw and hook anchor points can be planned depending on the curve type and degree of flexibility.

Thoracolumbar kyphosis may be corrected by a similar posterior approach, but requires a wedge excision of vertebral body or a subtraction osteotomy of pedicles, to allow sufficient movement for reduction of the deformity. An anterior release operation (e.g. via a thoracotomy) may need to be performed to allow sufficient movement to reduce the kyphosis.

Other approaches include thoracotomy and thoracoscopy for antero-lateral correction of a thoracic deformity, and the retroperitoneal approach to the antero-lateral lumbar spine. Indications for these approaches include congenital malformation of vertebrae, rigid deformities requiring release, pseudoarthrosis after posterior fixation, and in children less than 10 years old. Posterior fixation in the skeletally immature patient causes growth arrest of the posterior elements, but growth may continue at the vertebral endplates resulting in progression of the primary curve. For antero-lateral approaches, the convex side of the spine is exposed and screws placed into the vertebral bodies. The screwheads are attached to a rod, and compression of the screws then reduces the deformity.

Cranio-cervical junction anomalies

The pathophysiology of the cranio-cervical junction anomalies is complex. An important classification has been proposed by Menezes (1999), reproduced in Table 15.2. This subdivides the anomalies into congenital, developmental and acquired causes.

Table 15.2 Causes of craniovertebral anomalies.

Congenital anomalies and malformations
Occipital sclerotome malformations – atlas assimilation, proatlas remnants
Atlas malformations – bifid atlas, assimilation, fusion, absent arches
Axis malformations – segmentation defects, odontoid dysplasias
Developmental and acquired anomalies
Foramen magnum abnormalities
Foramen stenosis, e.g. achondroplasia (AD *FGFR3* gene)
Secondary invagination, e.g. ostoeogenesis impefecta, Paget's disease
Atlantoaxial instability
Down's syndrome
Metabolic disorders, e.g. Morquio's, Hurler's syndromes
Infections, e.g. Grisel's syndrome, tuberculosis
Trauma
Inflammation, e.g. rheumatoid arthritis, Reiter's syndrome
Tumour, e.g. osteoblastoma, neurofibromatosis, chordoma, meningioma
Miscellaneous, e.g. syringomyelia

AD, autosomal dominant.

Clinical features of cranio-cervical junction anomaly

There are three principal mechanisms by which the cranio-cervical junction anomalies lead to neurological signs. Frequently, more than one mechanism coexists.

Direct compression

This may result from developmental abnormalities of the odontoid process. Of particular importance is the condition os odontoidium where the odontoid and the body of the axis are not fused. Atlas assimilation, where there is failure of segmentation between the fourth occipital and first spinal sclerotomes, is relatively common and is particularly associated with the Chiari malformations. Direct compression may also result from abnormal articulation around cervical vertebral blocks as is seen in the Klippel–Feil syndrome.

Structural

Basilar invagination describes deformity of the osseous structures of the skull base that leads to upward displacement of the edge of the foramen magnum. In its primary congenital form it is often associated with platybasia where the clivus and anterior skull base are abnormally flattened. It may be associated with more subtle developmental bony anomalies and associated neurodysgeneses such as hindbrain herniation (particularly Chiari malformations) and syringohydromyelia. The foramen magnum itself may be narrow, usually as a feature of underlying skeletal dysplasia, as in achondroplasia. Acquired forms of basilar invagination are more common and result from any bone softening condition. The most important causes are osteogenesis imperfecta and Paget's disease. Diagnosis of basilar invagination on cervical spine X-ray historically involved measuring the position of the odontoid tip with respect to either the foramen magnum itself (McRae's line) or from lines drawn between the roof of the hard palate and either the posterior lip of the foramen magnum (Chamberlain's line) or the caudal part of the occipital bone (McGregor's line), although now a precise diagnosis is more commonly made by computed tomography (CT) or MRI scan (Figure 15.4).

Atlanto-axial instability

Atlanto-axial dislocation results from incompetence of the transverse ligaments or abnormalities of the dens itself. Instability is defined by an atlanto-dens interval >4 mm, and is demonstrated by flexion/extension X-rays of cervical spine or sagittal CT reconstruction. Three-dimensional CT allows assessment of any rotational component. Instability may occur spontaneously or develop secondarily to inflammation or trauma. It is a recognized feature of the complex developmental cranio-facial and cranio-vertebral anomalies, particularly if there is atlas assimilation and segmentation failure as in the Klippel–Feil syndrome. Syndromes that are also associated with ligamentous laxity carry a particular risk of dislocation, e.g. the mucopolysaccharidoses and Down's syndrome.

The surgical treatment of cranio-cervical junction anomoly is complex and complete description is beyond the scope of this

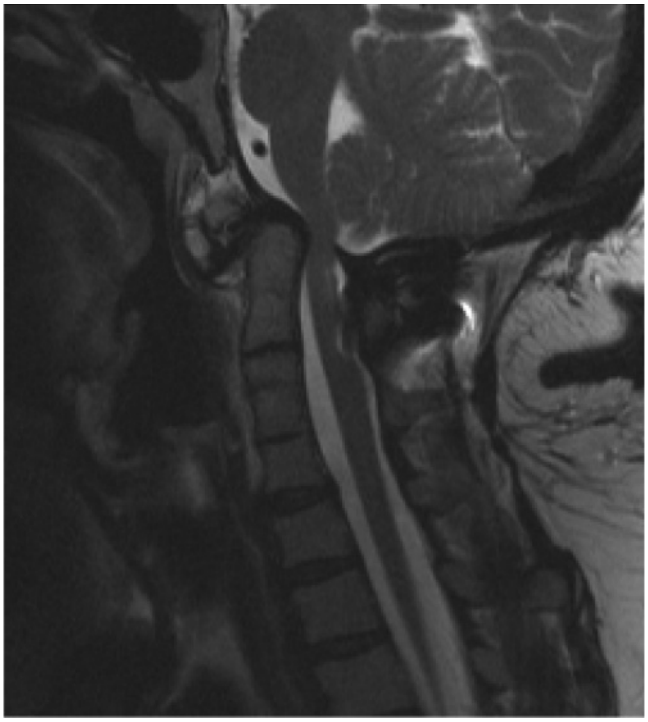


Figure 15.4 Congenital basal impression. Odontoid peg compression at cranio-cervical junction (MRI T2W).

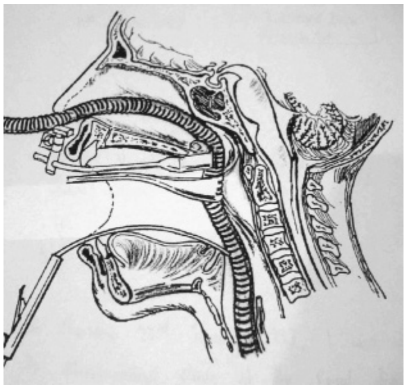


Figure 15.5 Transoral surgical approach to the cranio-cervical junction.

chapter. If neurological symptoms and signs of brainstem compression occur, or abnormal movement at C1–2 generates significant pain, then surgery is usually indicated. The aim of surgery is twofold: first to decompress and secondly to stabilize the cranio-cervical junction when necessary. Anterior decompressive surgery is commonly performed by the transoral approach, e.g. for tumours, rheumatoid pannus, os odontoideum and non-united odontoid fractures (Figure 15.5). Posterior decompression may be performed for Chiari malformations.

Horizontal atlantoaxial instability is commonly treated by posterior C1–2 fixation and bone graft, whereas vertical instability or 'cranial settling', analogous to a toffee apple on a stick, requires posterior occipito-cervical fusion.

Down's syndrome

Trisomy 21 occurs in around 1/650 live births and is the single most common cause of severe learning difficulties. It initially presents with characteristic dysmorphic features and hypotonia, often with associated cardiac and gastrointestinal anomalies. It is estimated that up to 25% of patients with Down's syndrome have asymptomatic atlanto-axial instability. Only around 1% are symptomatic. Recognized presentations include mild pyramidal tract signs with gait disturbance or the precipitous onset of cord compression. In the absence of signs or symptoms, screening of the atlanto-dens interval is no longer routine.

Chiari malformations

Professor Hans Chiari, an Austrian pathologist (1851–1916) described four types of hindbrain malformation.

The Chiari I malformation is demonstrated on neuroimaging by the dorsal extension of the cerebellar tonsils below the level of the foramen magnum. The prevalence of Chiari I in asymptomatic individuals is probably less than 1%, although it rises if tonsillar descent on sagittal MRI is associated with appropriate symptoms or other hind brain anomalies and in around 50% of cases of true cerebellar ectopia there is elongation of the medulla. Approximately 50% of Chiari I malformations are associated with cranio-cervical anomalies and syringomyelia. The development of Chiari I is likely to be multifactorial. It has been postulated on the basis of familial aggregation that Chiari I is a disorder of para-axial mesoderm. Chiari I is present in renal-coloboma syndrome in which mutations in the *PAX-2* gene have been identified. However, unlike Chiari II-IV there are clear examples of acquired Chiari I in which serial MRI has demonstrated postnatal development of the anomaly. Furthermore, lowering of CSF pressure following lumbar puncture or lumbar peritoneal shunting may be a risk factor for cerebellar tonsil descent. Chiari I has occurred during baclofen-pump insertion. There are well-documented examples of 'Chiari' or 'pseudo-Chiari' malformations improving following treatment of abnormally low CSF pressure caused by CSF leakage (Figures 15.6 and 15.7).

The symptoms and signs resulting from Chiari I overlap with those associated with other cranio-cervical anomlies (see above). These include headache, especially cough headache, nystagmus and quadriplegia. Additional symptoms and signs may result from associated hydrocephalus or syringomyelia. The condition is rarely symptomatic in childhood. Unusual presentations of Chiari I have been described: sudden death, syncope, ventricular fibrillation resulting from head movement, lingual myoclonus, pulsatile tinnitus, Ménière-type symptoms, acquired esotropia, central apnoea and paroxysmal rage.

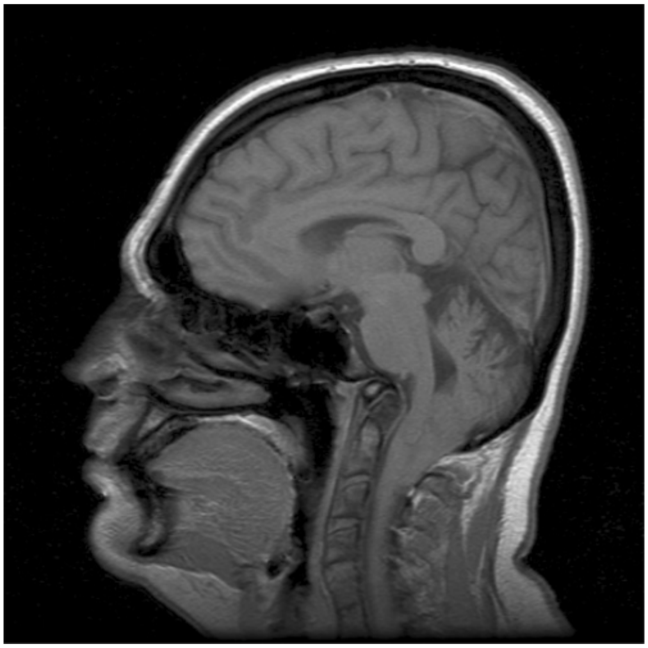


Figure 15.6 Chiari I malformation. MRI showing pre-operative appearances.

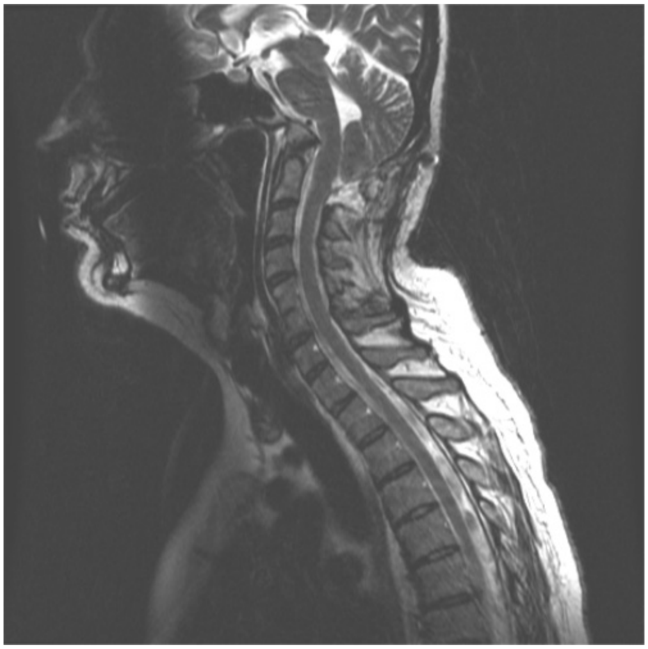


Figure 15.7 Chiari I malformation. Post foramen magnum decompression of patient whose scan is shown in Figure 15.6 (MRI T2W).

Chiari II malformation is a congenital anomaly that is associated with myelomeningocoele and hydrocephalus in >90% of cases and generally manifests in the neonatal period. It consists of caudal displacement of the medulla and cerebellum (particularly vermis) into the cervical canal over-riding the spinal cord often accompanied by partial herniation of the fourth ventricle and distortion of midbrain tectum. Associated abnormalities of supratentorial and midbrain structures are common.

Chiari III is analogous to type II but describes downward displacement of the cerebellum into a posterior encephalocoele, again with elongation and herniation of the fourth ventricle. Clinical features are severe and often life-threatening, particularly where there is cranial nerve dysfunction.

The Chiari IV malformation describes cerebellar hypoplasia and on current understanding is not part of the Chiari spectrum.

Asymptomatic Chiari I malformations may be treated conservatively. There have been case reports of sudden death in some patients with untreated malformations, but majority of these were not truly asymptomatic. Pregnancy in patients with significant Chiari I needs to be monitored and managed with care. Pushing during the second stage of labour causing further tonsillar descent and inadvertent dural puncture during epidural anaesthesia producing coning are two risks that need to be carefully considered. Some neurologists and neurosurgeons recommend that the baby be delivered by caesarean section and under general anaesthetic. Planned pregnancy is not an indication for prophylactic foramen magnum decompression.

Surgical treatment involves decompression of the foramen magnum and should be offered on the basis of significant and relevant symptoms, e.g. severe cough headache, or the presence of physical signs indicating neurological compromise. Posterior suboccipital decompression is the standard surgical management for symptomatic malformations, although there is much debate over how much bone to remove, whether the dura should be opened, scored or left intact, whether to use a dural patch graft or leave the dura widely open, and whether to resect the cerebellar tonsils to encourage good CSF flow. Surgery aims to prevent progression of symptoms, and improvement is seen in more than 80% of patients. Coexistent hydrocephalus usually improves after decompression of the foramen magnum, but if persistent, ventriculo-peritoneal shunting may be performed. Persistent syringomyelia may be treated by syringostomy, or by syringo-subarachnoid, syringopleural or syringoperitoneal shunting. After foramen magnum decompression it may take several weeks for a patient to become accustomed to their altered CSF dynamics, and the patient may feel unsteady or experience low-pressure headaches. Aseptic meningitis occurs in a minority, and usually responds to a tapered course of steroids over a few weeks, after a diagnostic lumbar puncture has been performed to exclude infection.

Syringomyelia

A syrinx is a cystic cavity in the spinal cord (syringomyelia) or brainstem (syringobulbia) which is lined by spinal cord parenchyma, as distinct from a cystic cavity which is in continuity with the central canal and lined by ependymal cells (hydromyelia). It is caused by abnormal transmission of raised CSF pressure through the spinal cord parenchyma during coughing and raised

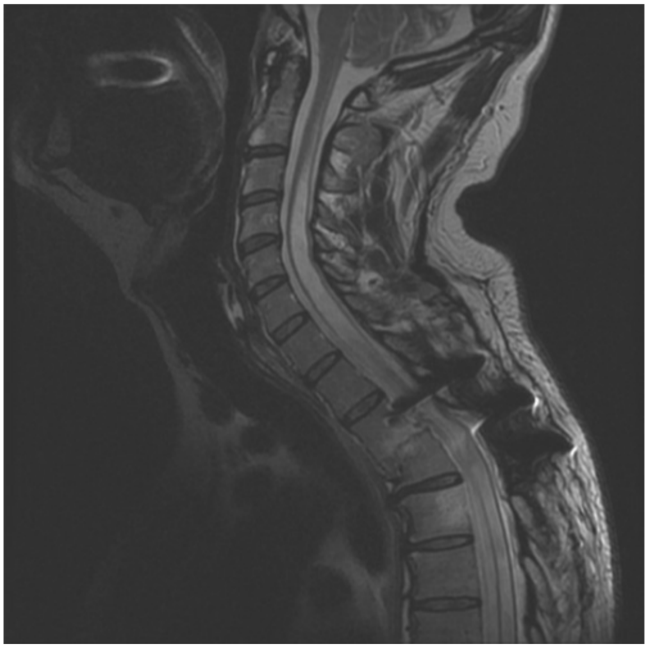


Figure 15.8 Syringomyelia. Post-traumatic cervico-thoracic syrinx (note T2–3 trauma and artefact resulting from pedicle screws) (MRI T2W).

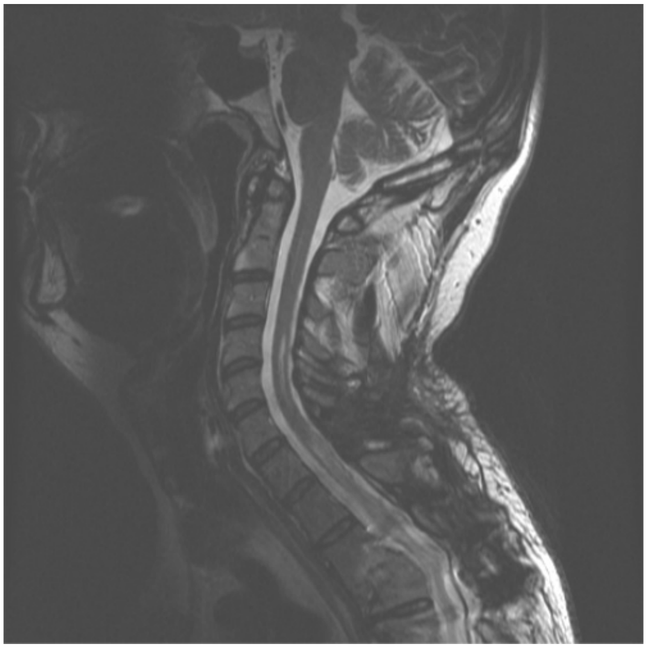


Figure 15.9 Syringomyelia. Imaging of patient whose scan is shown in Figure 15.8 following insertion of syringopleural shunt resulting in successful syrinx decompression (MRI T2W).

intra-abdominal or thoracic pressure, as a result of pathologically altered CSF dynamics. Syringomyelia may be caused by several conditions:

1 Trauma, with or without spinal cord injury, often with spinal deformity. Around 2–8% of patients with spinal cord injury develop a syrinx over time, usually several years after the injury.

2 Congenital conditions such as Chiari malformations, basilar invagination and Dandy–Walker syndrome.

3 Tumours, especially intramedullary tumours such as astrocytomas and ependymomas. Investigation of syringomyelia should always include a gadolinium-enhanced MRI to exclude a tumour as the cause.

4 Arachnoiditis, particularly when affecting thoracic and cervical spine.

5 Spinal infections.

The symptoms and signs of syringomyelia typically progress gradually over time, and are discussed in the section above. Diagnosis is usually made from the clinical features and typical appearance on MR imaging of the spine (Figure 15.8). A cause for the syrinx, e.g. Chiari malformation, spinal tumour or arachnoiditis, should be actively sought.

Treatment of syringomyelia

Non-progressive post-traumatic syringomyelia or hydromyelia causing mild clinical features is best managed conservatively. Progressive symptoms of syringomyelia need to be treated. As far as possible, the cause of the syrinx should be treated first, e.g. posterior fossa decompression for Chiari malformation. If the syrinx progresses and is symptomatic, treatment may include percutaneous drainage or open syringotomy. However, these techniques are associated with a high rate of syrinx recurrence, and a more permanent measure is to shunt the syrinx to the subarachnoid space, pleural or peritoneal cavities (Figure 15.9). Seventy-five per cent of patients were stabilized or improved in one surgical series, but because of the rarity of the condition and the variability in the surgical techniques available it is difficult to compare the outcomes of specific surgical options.

Congenital basilar invagination

Congenital basilar invagination results from a defect in the development of the cartilaginous skull base, producing elevation of the foramen magnum in relation to the occipital bone, with invagination of the lip of the foramen, along with flattening of the angle between the clivus and anterior fossa floor. This may be associated with other anomalies including occipitalization of the atlas, Klippel–Feil segmentation defects, Chiari malformation and syringomyelia. Basilar invagination should be distinguished from basilar impression, which is an acquired vertical translocation of the odontoid process into the foramen magnum occurring in conditions such as rheumatoid disease. Basilar impression is not usually associated with moulding of the skull base.

Os odontoideum

Congenital atlanto-axial instability is sometimes caused by aplasia or hypoplasia of the odontoid process, but is more commonly the result of an os odontoideum. This is an independent ossicle located above the centrum of the axis vertebra in the position of the odontoid process, which may be associated with a hypoplastic or completely absent dens. The abnormality is more common in Down's syndrome, spondylo-epiphyseal dysplasias and Morquio's syndrome. The cause is thought to be *in utero*, neonatal or childhood fracture of the odontoid process with subsequent non-union and remodelling. If there is significant instability in a physically active patient, surgical fusion of C1 and C2 is recommended to minimize the risk of damage to the spinal cord in the future. Radiological instability is seen in 15–30% of people with Down's syndrome, but instability is symptomatic in only 1–2% of patients. The current recommendation for patients with Down's syndrome and atlanto-axial instability is to restrict sporting activities if asymptomatic and to fuse patients who develop symptoms.

Spinal dysraphism

Spinal dysraphic states are caused by localized failure of neural tube closure during fetal development. Myelomeningocoele is the most common form, with an incidence of 0.8/1000 live births. Neural tube defects are caused by a variety of mechanisms: chromosomal abnormalities, single gene defects and teratogens. There are marked regional variations in its incidence and the condition is heterogeneous. There are strong genetic components and recurrence risks rise from 1–2% after one affected child to 10% with two affected children. Certain polymorphisms in genes involved in gene repair and folic acid metabolic pathways are associated with an increased risk of neural tube defect. The process of neuralation may be disrupted by teratogenic agents and in particular by maternal and/or fetal folate deficiency. Early folic acid supplementation reduces the incidence of neural tube defects, so that all women are recommended to take supplemental folate prior to conception and during the first trimester. It is estimated that approximately 70% of neural tube defects are preventable through maternal folic acid supplementation (400 μgm/day). This advice is especially important for women with a previously affected pregnancy or those taking anticonvulsants in whom the incidence of neural tube defects is around 1% of pregnancies; larger amounts of folic acid are recommended for these women (5 mg/day). Folic acid supplementation should be started preconception. Routine antenatal screening provides a prenatal diagnosis in many cases; raised maternal serum α fetoprotein is associated with open neural tube defects and fetal ultrasonography allows cranial and vertebral structures to be visualized directly. Prenatal counselling and pregnancy termination can then be offered.

Myelomeningocoele and myeloscisis comprise 95% of cases of spinal dysraphism, with exposed neural tissue a common feature. In a meningocoele and in spina bifida occulta neural elements are covered by skin. The clinical features are determined by the extent of the myelocoele and the presence of associated abnormalities, which may include both neural and extraneural anomalies. Progressive hydrocephalus requiring surgical treatment is present in 90% of cases and around 70% have a Chiari II malformation. Learning difficulties are common, one-third have an IQ < 80. Syringomyelia is present in up to 75% of cases and is often associated with severe scoliosis. Approximately one-third of patients have diastematomyelia.

Approximately 80% of open spina bifida defects are located in the lumbosacral area. The sensory level indicates the upper level of the lesion. Lesions above L3 result in complete paraplegia, but motor deficits may otherwise be patchy with a mixed pattern of upper and lower motor neurone signs. Sphincter and detrussor function is always compromised and careful urological assessment is required. Surgical closure is undertaken within 48–72 hours of delivery to reduce the risk of ascending infection and protect viable neural tissue within the placode. Following closure delayed hydrocephalus is likely. Patients generally require ongoing medical care by a multi-disciplinary team.

Spina bifida occulta describes occult dysraphism, where neural structures have not herniated through the mesenchymal defect. It includes diastematomyelia, terminal myelocystocele and tight filum terminale. Lipomyelomeningocoele and dermal sinuses are often included in this classification as they also result from abnormal secondary neurulation. Spina bifida occulta is often neurologically asymptomatic. The majority of patients have associated cutaneous abnormalities such as a tuft of hair or a dimple over the region, and plain X-rays show underlying vertebral anomalies. MRI scan then confirms the diagnosis. Two neurological presentations are recognized. First, a congenital asymmetric weakness and atrophy of the lower limbs and second the 'tethered cord syndrome' with progressive and sometimes precipitous onset of weakness and spasticity. The latter often presents in childhood or during the adolescent growth spurt and is an important cause of toe walking in childhood. Both presentations may be associated with sphincter disturbance. Treatment is primarily neurosurgical, with release of the spinal cord from the tethering lesion, with full preoperative neurological and urological assessment. Orthopaedic, othortic and physiotherapy management of lower limb deformity is also important.

Klippel–Feil syndrome

Described by Maurice Klippel and André Feil (Paris, 1912), the disorder is characterized by a short neck, impaired neck mobility and a low hairline. The incidence is approximately 1/42,000 births. Three types of Klippel–Feil syndrome are described. Skeletal abnormalities include fusion of two or more cervical or cervico-thoracic vertebrae (Figure 15.10). The syndrome is heterogeneous; differing numbers and positions of fused vertebrae

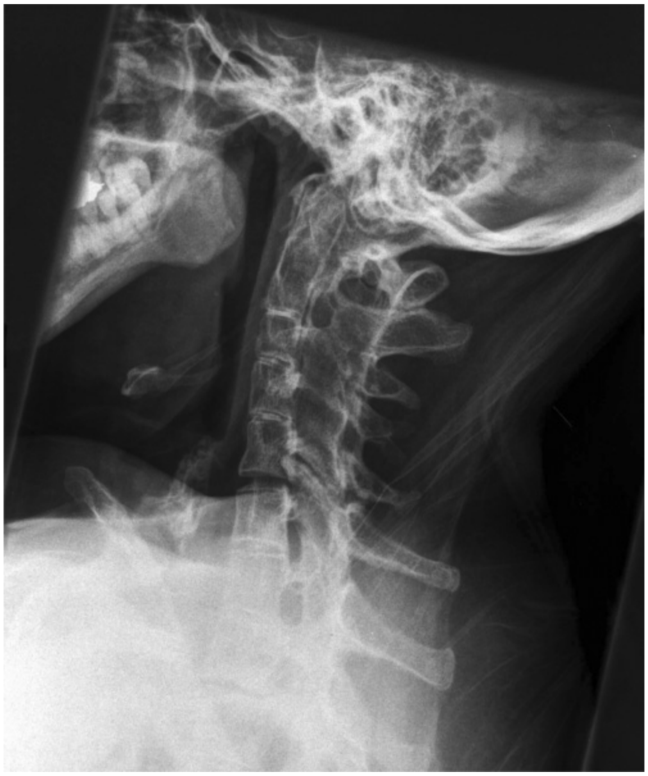


Figure 15.10 Lateral X-ray of patient wih Klippel–Feil syndrome showing vertebral segmentation anomaly.

are described and the associated anomalies are highly variable. The condition may be familial: dominant, recessive and X-linked inheritance patterns have been proposed; mutations in the *PAX1* gene may be associated with the condition. Despite the sometimes dramatic spinal abnormalities, a follow-up study over a 10-year period has indicated that only 20% of patients experienced significant cervical spine symptoms; only 6% required surgical intervention.

Extravertebral anomolies associated with Klippel–Feil syndrome affect multiple systems. Skeletal and systemic abnormalities include: scoliosis, scapula elevation, rib anomalies, cranio-facial dysmorphology, pulmonary, cardiac, gastrointestinal and urogenital anomalies. Neurological problems include syringomyelia, cranial nerve abnormalities, Duane's retraction syndrome, deafness, acquired myelopathy resulting from the spinal abnormality, thin corpus callosum, split cervical spinal cord (Figure 15.11) and failure of pyramidal tract decussation. The latter anomaly is particularly interesting as it may underlie the intense congenital mirror movements that affect a number of these patients.

Congenital mirror movements

These are intense involuntary movements, primarily of distal upper limb muscles, which mirror the voluntary unilateral movement. They cannot be suppressed and typically do not occur during passive movement. Mirror movements occur normally during a child's motor development, however, they are rarely intense and disappear by the age of 6 years. Pathological mirror movements are rarely disabling and patients learn adaptive proximal movements so as to avoid inappropriate finger movements, e.g. wrong key strikes while typing. Neurophysiological study of mirror movements has provided new insights into central motor control and plasticity.

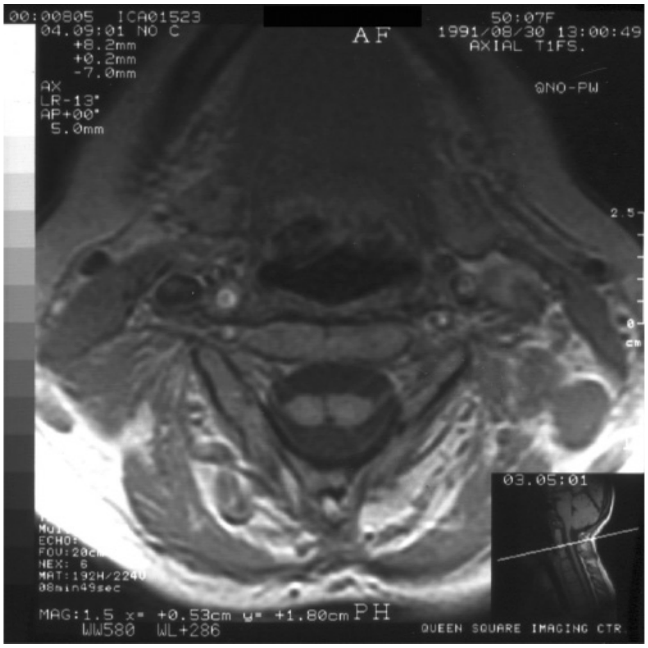
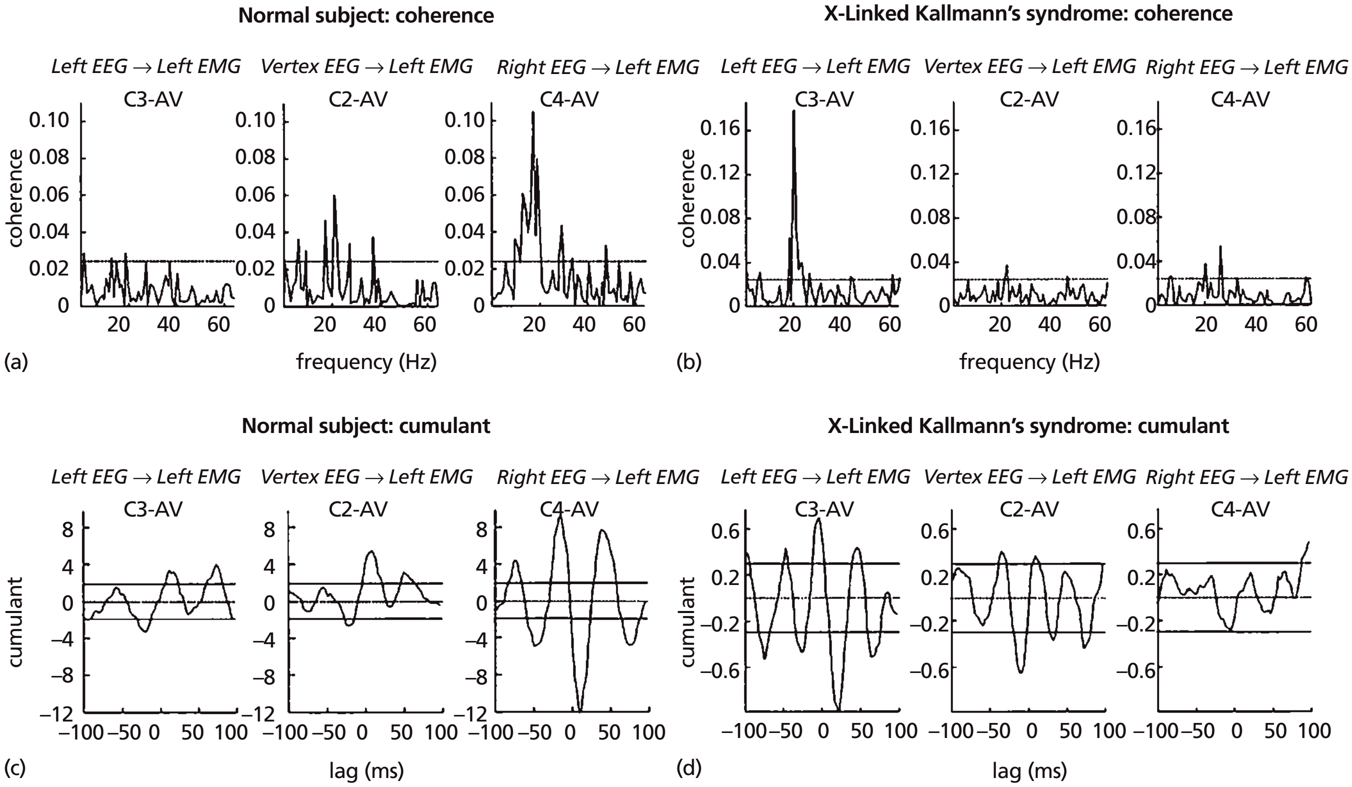


Figure 15.11 Split cervical spinal cord in patient with Klippel–Feil syndrome (MR axial).

A single subject with Klippel–Feil syndrome and mirror movements has been studied in detail. Unilateral focal electrical or magnetic brain stimulation (TMS) of either left or right primary motor cortex at threshold in non-mirroring subjects evokes contralateral short latency electromyographic (EMG) responses because of rapid conduction through pyramidal tract pathways. In contrast, mirroring individuals show simultaneous bilateral short latency EMG responses following unilateral motor cortex stimulation. Abnormal bilateral EMG responses indicate that in subjects with mirror movements the cortico-spinal tract is aberrant and bilaterally represented. In mirroring subjects the short latency (N20) component of the somato-sensory evoked potential is confined to the contralateral sensory cortex. Spinal (short) latency cutaneo-muscular (CMR) and stretch reflexes are confined, as in normal subjects, to the stimulated side. However, in mirroring subjects the long-latency components of the CMR and stretch reflexes are simultaneously present in both the stimulated and non-stimulated limbs. Cross-correlation analysis of EMG activity recorded simultaneously from homologous muscles of left and right hands reveals, in contrast to healthy subjects, the presence of a short duration peak at time zero indicating that during normal muscle contraction both hands receive abnormal common presynaptic drive. This abnormal drive can be shown to be highly muscle specific, indicating that abnormal bilateral cor-


Normal subject: coherence

X-Linked Kallmann's syndrome: coherence

Normal subject: cumulant

X-Linked Kallmann's syndrome: cumulant

Figure 15.12 Abnormal brain–muscle coherence and cumulant in subject with aberrant corticospinal tract. (a,c) Data from control subject with coherence and cumulant between right motor cortex electroencephalogram (EEG) and left hand muscle electromyogram (EMG). (b,d) Data from X-linked Kallmann's syndrome subject in whom transcutaneous magnetic brain stimulation showed abnormal ipsilateral fast conduction corticospinal pathways. In this subject there is abnormal coherence and cumulant between left motor cortex EEG and left hand EMG.

ticospinal axons innervate the equivalent motor neurone pools, e.g. those of first dorsal interosseous muscle on left and right sides of the spinal cord. This suggests that the abnormality is at the level of the pyramidal decussation with normal neuronal guidance mechanisms to the spinal motor neurone pools thereafter. Recent studies using EMG–EMG coherence analysis and EEG–EMG coherence analysis in subjects with X-linked Kallmann's syndrome with mirror movements have shown that aberrant corticospinal pathways provide abnormal oscillatory drive from cortex to muscle (Figure 15.12). Taken together, these findings indicate that voluntary and long-loop reflex activity in abnormal central motor pathways produces the mirror movements seen in Klippel–Feil syndrome and other neurodevelopmental conditions.

Intense mirror movements are a recognized feature of childhood hemiplegia and have been proposed to represent a physical sign of corticospinal tract rewiring following early brain damage. Children with hemiplegia and mirror movements have been studied using the approach outlined above for Klippel–Feil syndrome. The findings are similar except that the cortico-spinal axons reach both sides of the spinal cord from the undamaged motor cortex. The presence of mirror movements with characteristic neurophysiological findings is associated with MR imaging in which there is no gliosis in response to the cerebral injury, suggesting that antenatal insults before gestational age 28 weeks causing hemiplegia are associated with very significant pyramidal tract reorganization and mirror movements. This remarkable central nervous reorganization may help to sustain function of the child's hemiplegic hand, albeit at the expense of mirror movements. Recently, a patient with left hemisphere hydranencephaly (probably caused by a vascular insult at 20–27 weeks' gestation, i.e. after neural migration but before synaptogenesis) in which the entire left hemisphere was missing has been reported to be living a healthy, minimally affected life with a mild hemiparesis but otherwise excellent cognitive, motor and language function. This individual had strong mirror movements suggesting corticospinal reorganization and only on detailed testing could subtle prehension deficits be detected in the right hand.

Malformations of the pyramidal tracts

Consideration of the details of Klippel–Feil syndrome, X-linked Kallmann's syndrome and congenital hemiplegia pathophysiology has led to a wider appreciation of corticospinal tract development. While there are many tracts within the spinal cord, the

Table 15.3 Pyramidal tract malformations. (After ten Donkelaar *et al.* 2004.)

Induction defect	Cell proliferation	Neural migration	Guidance	Acquired
Anencephaly Encephaloceles Meckel–Gruber Apert ?Klippel–Feil	?X-linked Kallmann's syndrome Hemimegalencephaly	Lissencephaly Walker–Warburg Polymicrogyria Schizencephaly Zellweger's syndrome	X-linked hydrocephalus and other phenotypes associated with *L1CAM* mutations HGPPS (*ROBO3* mutations)	Hypoxic-ischaemic damage (e.g. hemihydranencephaly) Peri-venticular leucomalacia (PVL) Congenital infections

HGPPS, horizontal gaze palsy with progressive scoliosis.

normal development of which is crucial to function, much is known about the development and maldevelopment of the pyramidal tract and thus work in this area has led our understanding of developmental anomalies.

The pyramidal tract develops late in humans: in the embryo, fibres have reached the pyramidal decussation by the eighth week post-fertilization. Subsequent development is slow with tract myelination continuing into the third year of life. Our understanding of human pyramidal tract development is highly dependent on data from rodents and primates. In rat, the corticospinal growth cone must navigate through the internal capsule, cerebral peduncle, pons and medulla to reach the spinal grey matter. At a number of points in that journey there are 'choice points' at which chemo-attractants and repellents can influence the journey. Mutations in genes coding for these molecules lead to gross developmental anomalies. The corticospinal tract reaches the cervical cord shortly after birth and then gradually extends to the lumbar-sacral regions. Initially, there are exuberant collaterals such that most parts of the cortex, including the occipital cortex, innervate the cord. There is then a rapid withdrawal of collaterals and loss of fibres from the corticospinal tract. This process is activity-dependent; a functional lesion of one or other corticospinal tract will lead to persistence of ipsilateral projections from the intact corticospinal tract. Failure of pyramidal decussation occurs in a number of conditions including Klippel–Feil and X-linked Kallmann's syndromes. In animal models, mutations in oligodendrite membrane-bound neurite growth inhibitors appear to lead to loss of normal channelling of myelinated fibres leading to abnormalities of growth; furthermore, a midline anchored repellent (ephrin-B3) prevents the corticospinal tract from recrossing into the ipsilateral spine.

In humans, malformations of the corticospinal tract may be caused by:

1 Induction failure, i.e. disruption during early spinal development (see Klippel–Feil syndrome above);
2 Abnormal cell proliferation;
3 Abnormal neural migration;
4 Abnormal guidance mechanisms;
5 Acquired injury.

In all of these cases there are abnormalities of the pyramidal tract, the pyramids and the pyramidal decussation with abnormal ipsilateral cortico-spinal pathways. Mirror movements are a common feature of a number of these conditions and have been described in all the categories of pyramidal tract malformation set out below. The characteristic neurophysiology described in detail above for Klippel–Feil syndrome has been discovered also for X-linked Kallmann's syndrome, disorders of neural migration and prenatally acquired hemiplegia. In addition, ipsilateral TMS responses indicating an abnormal ipsilateral corticospinal tract have been described in patients with familial horizontal gaze palsy with progressive scoliosis (HGPPS). In these subjects, deletions in the *ROBO3* gene cause failure of pyramidal decussation. *L1CAM* disorders associated with a variety of phenotypes including X-linked hydrocephalus, have also been studied using TMS and, surprisingly, given that in animal models a misdirected pyramidal tract is usually the result of *L1CAM* mutations, no TMS evidence of an abnormal ipsilateral pathway was detected in humans. However, in the only neurophysiological study carried out, subjects with *L1CAM* mutations were not studied in the ways set out above, instead the focus of the investigation was on proximal rather than distal upper limb muscles. Table 15.3 shows examples of pyramidal tract malformation and misdirection.

Rheumatological disorders affecting the spine and spinal cord

Paget's disease

The disorder is rare before the age of 40 but becomes increasingly common with time, affecting 10% of 90-year-olds. The clinical features are those of bone pain, local deformity, bone enlargement, pathological fracture and a predisposition to sarcomatous change. The disorder often affects the skull and spine and as a result neurological involvement is common. Typical radiological appearances and the finding of an elevated serum alkaline phosphatase make the diagnosis of Paget's disease. The disease is one of excessive bone resorption with excessive osteoblastic and osteolytic activity. A genetic predisposition is described and some familial cases have been linked to chromosome 18q. A syndrome of Paget's disease with inclusion body myositis and dementia has been described. Pagetic osteoclasts contain nuclear inclusions and osteoclastic infection is one proposed mechanism although firm evidence for a causative paramyxovirus infection is lacking.

There are numerous potential neurological sequelae of Paget's disease. Direct compression by pagetic bone may lead to headache, dementia, brainstem and cerebellar dysfunction, cranial neuropathies, myelopathy, cauda equina syndrome and radiculopathies. The most common cranial neuropathy is sensorineural deafness. Optic atrophy, trigeminal neuralgia and hemifacial spasm may occur also. Pagetic softening of the skull may lead to basilar invagination resulting in brainstem and high cervical compression syndromes and occasionally hydrocephalus. The brain and spinal cord can become acutely compressed from epidural haematoma. The vascularity of pagetic bone may lead to cerebral ischaemia as part of a steal syndrome (compared to normal bone, blood flow in pagetic bone is increased threefold). Neurological syndromes may also develop because of compression of blood vessels.

Paget's disease generally responds to treatment with bisphosphonates although a relative resistance to these drugs is described. First line treatment is with potent oral bisphosphonates. Second line treatment regimes include calcitonin, etidronate and intravenous bisphonsphonates. Bone pain in particular can resolve within 1–2 weeks of commencement of treatment. Treatment efficacy may be monitored by serum alkaline phosphatase levels and a therapeutic response may be expected in approximately 80% of patients treated. Neurological syndromes often improve with medical treatment. Rapidly progressive neurological syndromes require high-dose intravenous bisphosphonate therapy and/or treatment with calcitonin. However, hydrocephalus generally requires shunting. Surgical decompression for basilar invagination, cranial nerve lesions, spinal cord and root compression is indicated if neurological symptoms and signs progress rapidly or despite best medical treatment. Medical treatment prior to surgical intervention may reduce bone vascularity and thus the risk of peri-operative haemorrhage.

Rheumatoid disease

Rheumatoid disease is a chronic inflammatory immune-mediated symmetrical polyarthritis with a predilection for the distal joints. Females are affected twice as commonly as males and the prevalance ranges from 0.2–2% of the population in Europe and North America. The inflamed synovium is termed the pannus; it is characterized by T- and B-cell activation, cytokine release, immune complex deposition, angiogenesis and cellular proliferation. This inflammatory process leads to damage and destruction of bone, cartilage and ligaments. Aggressive immunosuppressive therapy with disease-modifying drugs (in particular sulfasalazine and methotrexate) improves the prognosis of rheumatoid arthritis. The newer immune-modifying drugs, such as antitumour necrosis factor and anti-interleukin 1 agents, have improved the prognosis of the disease: compared to past decades, fewer rheumatoid patients are now presenting for surgery to the cervical spine and large joints.

Neurological manifestations of rheumatoid arthritis include entrapment neuropathy, vasculitic neuropathy, myopathy and ischaemic syndromes caused by vasculitis; these are discussed further in Chapter 25. The spinal cord manifestations result from ligamentous disruption, bone destruction and secondary osteoporosis. A rare syndrome of diffuse dural infiltration with inflammatory cells producing a pachymeningitis has been described.

Patients with rheumatoid arthritis of the cervical spine frequently experience headache and neck pain; however, the most feared neurological complication of rheumatoid arthritis is upper cervical cord and brainstem compression. Neurological symptoms usually result from one of three ways: atlanto-axial subluxation, basilar impression (vertical translocation) or subaxial subluxation.

Involvement of the atlanto-axial ligament often combined with local pannus formation and bone destruction produces subluxation. Atlanto-axial subluxation affects 25% of rheumatoid patients of whom 25% have neurological signs. Atlanto-axial subluxation may occur in lateral, rotational, anterior, posterior and vertical directions; the latter three directions being the most neurologically significant. Rheumatoid arthritis may affect the spinal cord caudal to the C1–2 level independently or in association with a high cord lesion. Postmortem studies of myelopathy show necrosis, gliosis and Wallerian degeneration within ascending and descending white matter. Cervical myelopathy is caused by repetitive minor trauma to the spinal cord because of excessive movement of the unstable level. The degree of atlanto-axial subluxation is well characterized by plain flexion–extension radiography; however, because a large part of the compression is caused by inflammatory soft tissue proper assessment requires detailed MR imaging.

Natural history

In a series of 235 rheumatoid patients referred for neurosurgical assessment of cranio-cervical junction instability, 60% had myelopathy, the majority of these either had motor or mixed motor and sensory long-tract signs; in approximately 10% the predominant deficits were loss of joint position and Rombergism, indicating a mainly posterior compression. Cranial nerve signs and nystagmus were rare and in this series were associated with other pathologies, especially Chiari malformation.

Rheumatoid arthritis initially involves the hands and feet, and large joints usually require surgery before the neck. Wolfe found that in the USA one in four patients had a large joint arthroplasty in the first 6 years of the disease and Casey *et al*. (1996) discovered that in their population, cervical disease required surgical treatment in patients who had had between two and four previous arthroplasties. This implies that greater degrees of mobility in rheumatoid joints leads to accelerated degeneration and instability. Hence, the cervical spine is affected commonly, particularly the atlanto-axial joint and the cranio-cervical junction, and the lower spine is usually spared. The percentage of rheumatoid patients who develop atlanto-axial subluxation varies between series, and is largely biased by the source of data collection. There are few large population-based cohort studies in the literature, but from non-surgical studies over the past few decades the percentage of rheumatoid patients with atlanto-axial subluxation varies from 14% to 73%, with an average incidence of 35% (21% horizontal and 14% vertical subluxation). More than 30% will have symptomatic atlanto-axial subluxation 5–7 years after the onset of the disease. Five per cent then become myelopathic a decade later, 14–17 years after onset. Once myelopathy has developed the outlook is poor, with up to 50% mortality within a year.

Indications for surgical management of the rheumatoid spine

A study of surgical outcome comparing the 1970s with the 1990s found an improvement in mortality from 9% to 0%, a decrease in complication rate from 50% to 22%, and improvement of symptoms in 89% of patients who had surgery. Improved outcomes have been a result of better instrumentation and the trend towards earlier surgery; it is now accepted that operations for non-ambulant myelopathic patients are associated with an unacceptably high complication rate, and poor functional improvement. Atlanto-axial fusion is now more commonly performed for instability causing pain, early neurological symptoms and signs, occipital neuralgia or progressive radiological appearances (Figure 15.13).

Selection of appropriate patients for surgical intervention presents a major clinical problem. The policy of waiting until rheumatoid patients with atlanto-axial subluxation develop signs of serious myelopathy has been strongly challenged on the basis that once spinal cord damage has been sustained it is rarely reversible. In a prospective trial it has been shown that following surgical stabilization, with or without transoral anterior decompression, approximately 60% of ambulant patients will show stabilization or improvement of their functional status; in contrast only 20% of non-ambulant patients will show any recovery. Furthermore, surgical morbidity and mortality was found to be significantly higher in the non-ambulant (12.7%) compared to the ambulant group (8.9%). In the past, major surgery was often performed for patients with end-stage myelopathy, often with poor results. Now surgical stabilization is generally performed at an earlier stage once instability has been demonstrated. Early surgery is associated with a better outcome, lower risk and prevents further deterioration in the diseased joint.

It should be noted that the combination of mild neurological impairment and rheumatological/orthopaedic problems puts rheumatoid patients at increased risk of falls and even minor cervical injury can produce catastrophic neurological deterioration. Atlanto-axial subluxation increases the anaesthetic risk because of neck extension during artificial ventilation (Table 15.4).

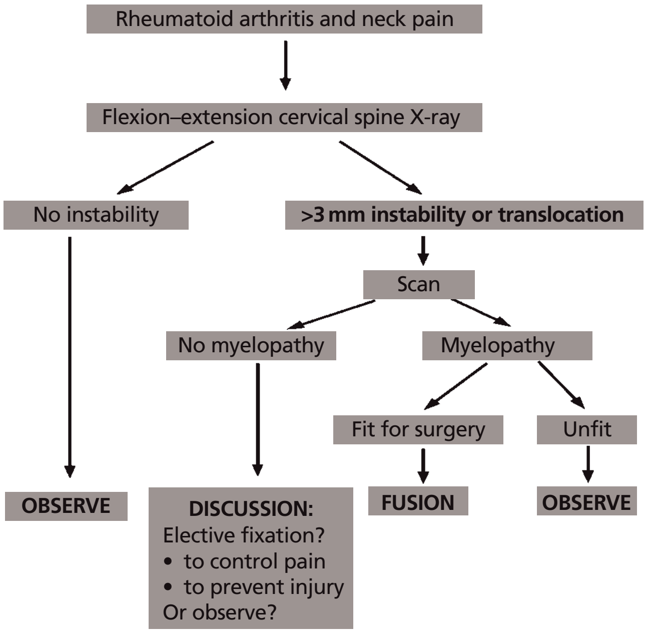


Figure 15.13 Algorithm for assessment and treatment of rheumatoid atlanto-axial disease.

Table 15.4 Indications for different types of surgical stabilization in rheumatoid disease.

C1–2 fixation should be considered for
Instability and intractable pain
Clinical myelopathy
Occipital neuralgia
Progressive radiological subluxation
Antero-posterior spinal cord diameter less than 6 mm on flexion MRI
PADI less than 10 mm on CT
Patients with instability who are unable to wear a hard collar or brace
Fixation of the occiput to cervical spine should be considered for
Vertical translocation
Excessive degeneration or instability of the occipito-atlantal joints
When C1 or C2 bone quality does not allow adequate screw purchase or fixation of a short segment
Disruption of the ring of C1 by fracture or after transoral odontoidectomy
When there is a significant 'stair-case' deformity or instability in the subaxial spine, requiring a longer construct to simultaneously fuse lower levels
Transoral decompression and posterior fixation should be considered
When there is irreducible atlanto-axial subluxation causing ventral compression of the neuraxis
When there is marked vertical translocation (>5 mm) causing brainstem compression
When an anterior soft tissue mass causes compression around the cranio-cervical junction

MRI, magnetic resonance imaging; PADI, posterior atlanto-dental interval.

Spondyloarthropathies

The inflammatory spondyloarthropathies include ankylosing spondylitis, psoriatic arthritis; arthritis associated with inflammatory bowel disease and reactive arthritis, e.g. Reiter's disease. Low back pain is common to all conditions. The primary neurological manifestations are best represented through consideration of ankylosing spondylitis, although they may also occur in association with the other spondyloarthritides.

Ankylosing spondylitis is the most prevalent of the seronegative spondyloarthritides, affecting up to 2% of the population in the West. It usually presents with gradual onset low back pain and stiffness of the large joints. The condition can affect other organ systems. Men are affected more than women. Disease onset is typically before age 40. HLA B27 is strongly associated with >90% of patients expressing the antigen. Unlike rheumatoid disease, it commonly affects the spine and sacroiliac joints, rather than the peripheral joints, and the disease progresses in a caudal–rostral direction, resulting in flexion deformities in posture. The pathological hallmark is the development of enthesopathy, that is inflammation around sites of tendinous insertion. Syndesmophytes form in the spinal column points where spinal ligaments attach to the vertebral bodies.

The neurological manifestations of ankylosing spondylitis are usually a late stage complication. Loss of spinal movement is associated with vertebral body squaring and extensive loss of ligamentous laxity because of syndesmophyte formation. This process produces a rigid spine with kyphosis. Spinal involvement may produce atlanto-axial subluxation, pathological vertebral fracture, disco-vertebral destruction, spinal canal especially lumbar canal stenosis and a cauda equina syndrome. Atlanto-axial subluxation occurs more rarely than in rheumatoid arthritis; however, the management issues are similar. Spinal rigidity and disco-vertebral problems predispose to cord compression. Acute spinal cord compression resulting from epidural haematoma is a recognized problem. Spinal fractures are more common because of the rigidity of the spine, and the use of a rigid collar in the emergency department is often prevented by the degree of kyphotic deformity. Forcing the neck into a collar can itself result in a cervical fracture. Despite the tendency to ankylosis in these patients, conservative management often results in a pseudoarthrosis, and anterior or posterior fusion with surgical fixation is required.

The cauda equina syndrome is a rare late stage complication of ankylosing spondylitis. It presents gradually with leg pain, leg weakness, sensory disturbance and sphinteric dysfunction. On imaging studies posterior lumbar-sacral diverticulae are present. An arachnoiditis may also contribute to the development of the cauda equina syndrome; however, the presence of the diverticulae indicates that ankylosing spondylitis is the likely cause rather than some other form of arachnoiditis (Figure 15.14). It is important to remember that spinal irradiation was used to treat ankylosing spondylitis and late radiation neurological damage and bone sarcoma may result.

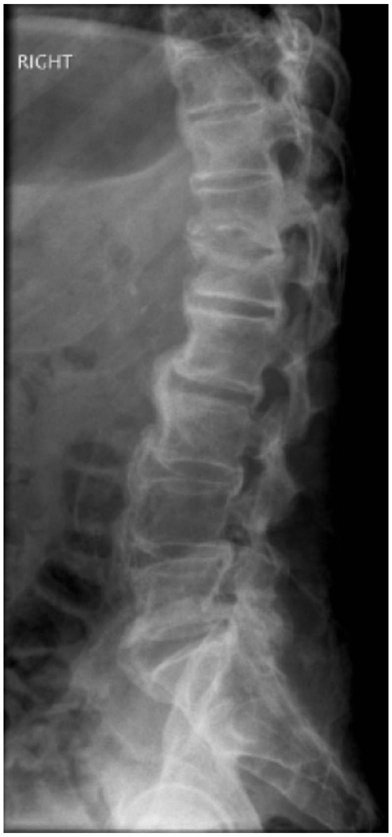


Figure 15.14 Lateral X-ray of thorocolumbar spine in a patient with ankylosing spondylitis.

Miscellaneous conditions affecting the spine and spinal cord

Superficial siderosis

This is a condition in which there is abnormal subarachnoid haemosiderin deposition (Chapter 16). The condition affects many neurological systems and when taken together the symptoms and signs form a coherent and recognizable clinical picture. A literature review of 87 cases revealed the following clinical features: sensorineural deafness (95%), cerebellar ataxia (88%), pyramidal signs (76%), dementia (24%), bladder disturbance (24%), anosmia (at least 17%), aniscoria (at least 10%) and sensory signs (13%). Less frequent features included extraocular motor palsies, movement disorders and lower motor neurone signs secondary to anterior horn cell damage (5–10% each). Neck pain, low back pain and sciatic type pain are recognized clinical features. T2-weighted MRI studies of these patients reveal a dark rim, representing the paramagnetic affects of iron deposition, particularly around posterior fossa structures, the spinal cord and occasionally the cerebral hemispheres.

Previous spinal surgery is a recognized cause of superficial siderosis with chronic subarachnoid bleeding resulting from small

Table 15.5 Causes of superficial siderosis.

Neurosurgery	Including late effects following CNS tumour removal in childhood
SAH	Caused by aneurysm, AVM or angiogram negative; SAH due to Transthyretin (Asp18Gly TTR mutation) leptomeningeal amyloidosis; intracerebral and spinal cavernomas
Tumours	Pituitary, cerebellar, spinal astrocytomas, spinal teratoma, ependymoma, filum terminale preganglionomas, spinal meningeal melanocytoma
Nerve root trauma	Avulsion, pseudomeningocoele
Miscellaneous causes	Neurofibromatosis Type 1, CNS vasculitis, anticoagulation

AVM, arteriovenous malformation; SAH, subarachnoid haemorrhage.

Table 15.6 Causes of arachnoiditis.

Iatrogenic: spinal surgery, multiple lumbar punctures and spinal anaesthesia
Trauma
Subarachnoid haemorrhage (SAH) including spinal SAH
Spinal infection, especially tuberculosis and suppurative pyogenic meningitis
Myodil (Pantopaque) radiological contrast agent (this has not been used in the UK since 1984)

blood vessel anomaly. Local spinal pathology affecting the dura such as a root lesion/avulsion or vascular anomaly are also recognized causes of the condition. The remainder of cases in which a cause may be identified usually result from subarachnoid haemorrhage or the late consequences of a major neurosurgical procedure such as hemispherectomy. However, as shown in Table 15.5, there are a number of case reports implicating a variety of conditions in the development of superficial siderosis. The serious long-term prognosis of the disorder means an exhaustive search for a bleeding source should be undertaken. This may involve exploratory surgery of a region from which chronic bleeding might possibly occur, e.g. the site of previous surgery. Successful surgical ablation of a bleeding source may arrest the condition. The role of medical treatment with chelation therapy (trientene) is not established. However, anecdotal accounts suggest such treatment may have a role in slowing disease progression. Cochlear transplants have been successfully performed for the hearing loss associated with siderosis.

Arachnoiditis

Fibrosis and adhesions of the intradural space may occur after trauma, infection, surgery or subarachnoid bleeding, and usually involve the pia and theca as well as the arachnoid layers around the cord (Table 15.6). Radicular symptoms may arise because of involvement of the lumbar nerve roots, or myelopathy if the cord becomes tethered by these adhesions at any point.

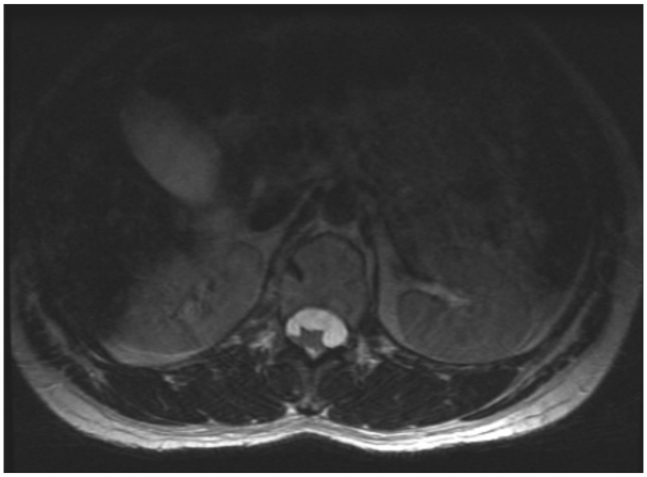


Figure 15.15 Arachnoiditis deforming thoracic cord (axial MRI).

The diagnosis involves the exclusion of other causes of radicular pain or myelopathy, and the demonstration of arachnoiditis on MRI. The differential diagnosis includes intrinsic tumours and carcinomatous meningitis. Radiological arachnoiditis is seen in many asymptomatic patients who have had spinal surgery or myelography, and there is no clear evidence to associate radiological findings directly with symptoms. In postoperative patients therefore, arachnoiditis should not necessarily be assumed to be the cause of new symptoms.

In the lumbar region, nerve roots adhere to form bundles, or lie centrifugally in contact with the thecal sac, producing the appearance of an empty sac. In the thoracic spine, arachnoiditis produces intra-medullary cystic changes with syrinx and cavity formation. The MRI appearances can be confusing (Figure 15.15). When arachnoiditis occurs in the thoracic regions, the cord may be tethered to the theca, e.g. at the point of surgical durotomy, or may produce arachnoid cysts as a result of poor communication of the CSF spaces.

Surgical de-tethering may treat a tethered cord in a patient with progressive neurological symptoms. Arachnoid cysts producing cord compression may be marsupialized or shunted but the problem is often recurrent. Lumbar arachnoiditis producing radicular pain is usually best treated by symptomatic control, including epidural injections of local anaesthetic and steroid, pain management techniques and analgesics. Despite attempts to inhibit fibrosis as yet no successful medical therapies capable of reversing arachnoiditis have been developed.

Spinal cord injury

> 'The person dies instantly when the spinal cord is pierced . . . and therefore it would seem lies the foundation of movement and life.'
> Leonardo da Vinci (1425–1579) *Quaderni d'Anatomica, Vol. V*

Few survivable injuries have as much impact on a patient's life as acute spinal cord trauma, and its associated human and social cost. The most common cause is vehicle accidents, followed by violent assault, falls and sports injury, especially high board diving. Severity of injury may be classified using the American Spinal Injury Association Score (ASIA) for quantitative assessment of motor and sensory function, or the ASIA/Frankel grading system, A–E for clinical grading:

- A: the most severe with no motor or sensory function below the level of the lesion with no preservation of sensation in sacral dermatomes S4–S5;
- B: 'incomplete' in which there is no motor function below the lesion but there is preservation of sensory function (in this group sacral preservation of pin prick indicates a better prognosis for functional recovery);
- C: 'incomplete' motor function is preserved below level of lesion (MRC <3);
- D: 'incomplete' motor function is preserved below level of the lesion with 50% muscles MRC grade 3 or above;
- E: normal motor and sensory function.

The majority of grade A patients will show some recovery of motor function (increase in one level) especially in the first 6 months although later improvement does occur. Between 20% and 30% of grade B patients recover to grade D or E, 50–70% of grade C patients recover to grade D or E. Ambulation is normally achieved in patients who recover to grade D. In severe spinal cord lesions the level of the lesion critically determines the functional outcome with preservation of arm function (lesion below C6) being important for maintenance of transfers and activities of daily living. Assisted ventilation is required for patients with severe spinal cord lesions above C3. Independence of bowel and bladder function, albeit with intermittent self-catheterization, may be expected if upper limb function is preserved.

Acute management

Resuscitation of the patient and treatment of life-threatening injuries are the initial priorities. Immobilization of the spine at the scene of the trauma, especially the neck, should be performed until the neurological and mechanical integrity of the spine can be established. A cervical injury should be assumed until proven otherwise in all patients with a significant force of injury or those who are unconscious.

The investigators of the National Acute Spinal Cord Injury Studies (NASCIS) advocated the use of methyprednisolone within 8 hours of the injury, a bolus of 30 mg/kg followed by 23 hours of IV methylprednisolone 5.4 mg/kg/hour. Its effects are not completely understood but as well as reducing oedema steroids may prevent lipid peroxidation, which disrupts myelin. Other drugs that prevent lipid peroxidation are also under trial. However, there is a body of evidence that the side effects of steroids outweigh the benefits in head injuries. The CRASH trial (Corticosteroid Randomization After Significant Head Injury) looked at the 6-month outcomes of over 10,000 randomized patients and found that mortality in those given high-dose steroids was increased compared to placebo. The majority of data from animal models for the use of steroids in spinal cord injury do not show a beneficial effect, and questions have been raised about the handling of data in the NASCIS 2 subgroup analysis. A systematic review of 157 studies of methylprednisolone infusion in spinal cord injuries concluded that there is insufficient evidence to support the use of steroids as a treatment standard. Opinions differ but at this point there is no clear evidence to support use of high-dose intravenous methylprednisolone during the acute phase of traumatic spinal cord injury.

Surgery should be performed for incomplete lesions with cord compression and progressive neurological signs, mechanical instability preventing mobilization, and if internal reduction of dislocation is required. Wound debridement may be necessary for dirty penetrating injuries. However, surgery will not improve a fixed neurological deficit that has been present from the time of injury.

The optimal surgical management of spinal fractures and cord injury remains controversial. Traditionally, patients were treated with 6–12 weeks of bed rest, traction and then mobilization with external orthotic stabilization. Proponents of conservative management argue that bed rest improves perfusion of the spinal cord at this very vulnerable stage following injury. Neurological outcome was studied in 63 consecutive patients with incomplete cervical cord injuries and was found to be dependent on the initial presenting neurological level of function. The neurological deficit at presentation and also the extent of recovery were not associated with the degree of spinal canal compromise. However, prolonged bed rest is associated with deep venous thrombosis, pulmonary embolism, chest infections, pressure sores and muscle atrophy. The development of titanium constructs and instrumentation over the past few decades have allowed surgeons to produce robust fixation and fusion at an early stage, facilitating early mobilization, vigorous physiotherapy and avoidance of these complications. A review of the evidence for surgical management of spinal injuries concluded that many animal studies and class II and III human studies supported early intervention in improving neurological outcome. However, there is no class I evidence to support conservative or surgical management of acute spinal injuries, and most clinicians seem to base their judgement on belief, logic and individual experience.

There is a significant trend towards early surgical intervention to minimize the risks of immobilization and maximize spinal stability for the future, as well as for reasons of health economics. Surgery should be performed in the controlled environment of the next available daytime list. The risks of surgery itself have decreased with the widespread use of modern technology and operating microscopes, and broadly speaking, there is a 1% chance of irreversible cord damage and a 5% chance of other problems including infection, failure of fusion and anaesthetic risks.

Central cord contusion of the cervical spine without instability may occur, especially if there is a background of spondylotic spinal canal stenosis. Some surgeons recommend non-operative management of these patients because of the theoretical risk of worsening their function if surgery is performed within 4–6 weeks of the injury. The evidence for this traditional approach is weak, and originates from a small series of eight patients, two of whom deteriorated after surgery to decompress the cord and section the dentate ligaments. The authors recommend early surgery in this group of patients if there is no spontaneous improvement and the spinal cord is compressed, or if a patient improves but then deteriorates. If there is no active cord compression or instability, then early decompression is not warranted. Of patients with a central cord contusion and tetraplegia or severe paresis, 50% eventually walk again and sphincter control usually recovers but manual dexterity tends to recover less satisfactorily.

Surgical management of spinal fractures

The authors advocate early internal stabilization once the patient is well enough, with reduction or decompression if required. Specific management is tailored to the patient, neurological and radiological findings.

Cervical fractures

Fractures of C1 may be caused by a vertical blow to the vertex of the head, resulting in at least two fractures of the ring of the C1 vertebra (Jefferson fracture). The fragments tend to displace outwards, and usually there is no neurological deficit. Jefferson fractures are usually managed by immobilization in a halo brace or rigid collar, depending on the degree of instability. Fusion is usually achieved by immobilization alone, and surgical fixation is rarely required.

Occasionally, rotation of a C1 facet may occur beyond the articular surface of the C2 facet below, resulting in rotatory subluxation and locking of the facet. This may occur because of trauma, in rheumatoid disease or may occur spontaneously, especially in children. Patients present with a characteristic 'cock robin' posture: rotation away from the dislocated side, slight flexion and lateral tilt towards the dislocated side, with contralateral spasm of the sternocleidomastoid muscle.

Reduction may be achieved by gentle traction and manipulation under anaesthetic, or if it is more long-standing, open reduction may be required, using the far lateral approach to the cranio-cervical junction.

Atlanto-occipital dislocation may occur with extreme longitudinal distraction, with or without horizontal dislocation of the cranio-cervical junction. This often results in cardiopulmonary arrest and death. Traction will worsen the situation. Treatment involves internal fixation

Fractures of C2 include the 'hangman's fracture' through the pars interarticularis of the C2 pedicles. The resulting spondylolisthesis is more commonly caused by hyperextension and axial loading during a road traffic accident. These fractures rarely cause a neurological deficit provided there is no significant dislocation, because the diameter of the spinal canal at C2 is effectively increased by the fracture. Instability is indicated by excessive subluxation or angulation of C2 on C3, which is exaggerated on flexion and extension X-rays. Reduction may be achieved by skull traction. Most of these fractures heal with immobilization using a halo brace or rigid orthosis. Surgery is indicated if the fracture will not reduce adequately, if there is cord compression, or if fusion is not achieved by non-operative measures. The most common operation involves an anterior approach, C2–3 discectomy, fusion and insertion of an anterior plate.

Road traffic accidents and falls from a height are a common cause of odontoid fractures in young people. However, they may occur in older people by seemingly minor falls, hitting the forehead on the ground. Acute symptoms are usually pain and occipital neuralgia, but cervical myelopathy may occur with long-standing fractures and instability. They may be classified into three types:

1. Type I fractures are through the tip of the peg, are rare, and usually stable;
2. Type II fractures are through the base of the peg, and are unstable. These are the most common peg fractures, and the least likely to fuse with immobilization alone.
3. Type III fractures involve the body of C2, are usually stable and heal with immobilization alone.

Surgery is usually indicated in type II fractures with excessive displacement of the peg (>4–6 mm in any direction), in older age groups when spontaneous fusion is less likely, or with chronic non-union of the fracture. Within 6 weeks of the accident, a type II peg fracture may be fixed with anterior odontoid peg screws (Figure 15.16), but after longer intervals soft tissue becomes interposed between the bone fragments and posterior C1–2 fixation and bone grafting is required (Figure 15.17). This latter operation will limit cervical rotation by 30%.

Injuries associated with hyperflexion and rotation of the neck can result in a unilateral facet joint dislocation in the subaxial cervical spine. Such patients are usually neurologically intact and do not exhibit instability on flexion–extension X-rays. However, extreme hyperflexion injuries may result in bilateral dislocation of the facet joints, usually associated with more extensive disruption of joint capsules, discs and posterior ligaments. CT scanning should be performed to inspect the integrity of the facets, and traction is used to reduce bilateral dislocations. If traction is unsuccessful, then open reduction is required, either by an anterior or posterior approach, followed by fixation and bone graft fusion.

Thoracolumbar fractures

The stability of thoracolumbar fractures is well described by the Denis three-column model. The spine may be considered as three columns of stability: the anterior, middle and posterior columns. The anterior column consists of the anterior half of the vertebral bodies, discs and the anterior longitudinal ligament. The middle column includes the posterior half of the vertebral bodies, discs and the posterior longitudinal ligament. The posterior column is made up of the facet joints, joint capsules, laminae, spinous processes and adjoining ligaments. Disruption of two of the three columns is considered to be mechanically unstable and probably

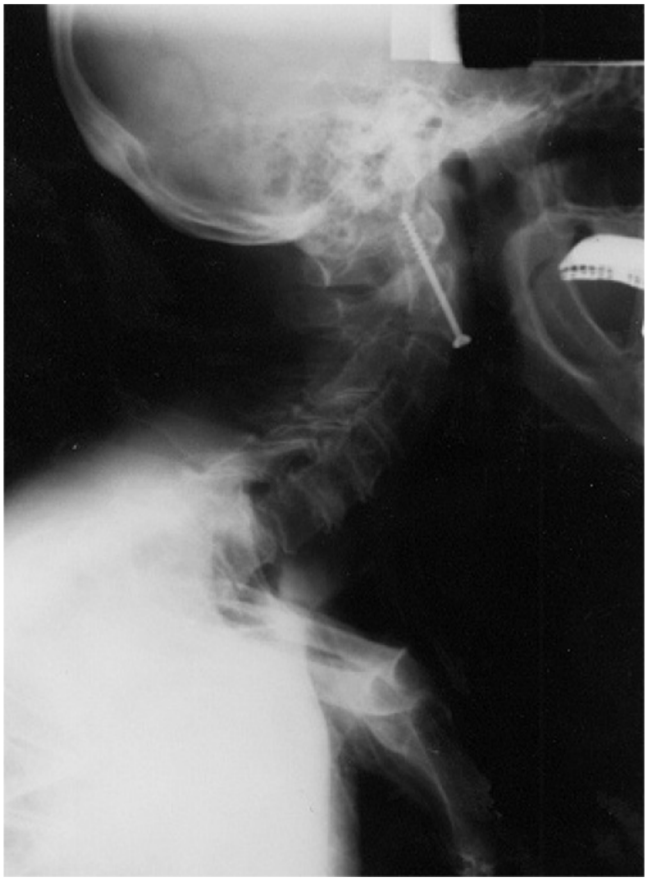


Figure 15.16 Lateral cervical X-ray showing a screw inserted to stabilize an acutely fractured odontoid peg.

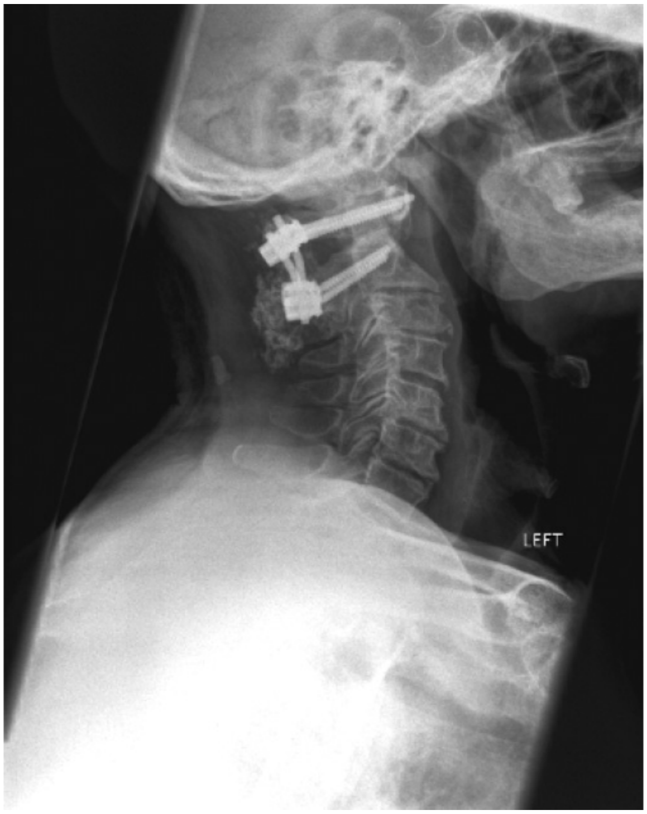


Figure 15.17 Lateral cervical X-ray showing C1–2 fixation for chronic odontoid peg fracture.

requires operative fixation, whereas disruption of a single column is likely to be stable and can be treated with bed rest. If surgery is required, posterior instrumentation with pedicle screws is the most common fixation technique, although thoracotomy or retroperitoneal approaches are sometimes required for stabilization of the thoracic and lumbar spines, respectively.

Non-surgical management of spinal trauma

Whiplash injury

Whiplash is a traumatic injury to the cervical soft tissues (including joint capsules, ligaments and muscles) resulting from hyperflexion or hyperextension, in the absence of fractures or instability. Symptoms of pain usually start several hours after the injury, and may be associated with tension headache and poor concentration. Diagnosis is by exclusion of instability, disc herniation or spinal cord injury. It is interesting to note the findings of a Lithuanian study, where few drivers have insurance and disability compensation is unlikely. In this survey there was no significant difference in the incidence of chronic neck pain in people who were involved in a road traffic accident and the general population.

Rehabilitation

Rehabilitation is covered in detail in Chapter 17. The primary goal of rehabilitation should be to increase functional capability, especially in walking and standing. Weight-supported treadmill training has shown promise in partial spinal cord lesions. In contrast to studies on the cat, at present there is little evidence in humans for a spinal central pattern generator that in the absence of descending control will drive limb movements and posture capable of supporting functional gait. Spinal pattern generators are favourably influenced by afferent feed back from the limbs and centrally by neurotransmitters, especially adrenergic transmitters. This raises the possibility that functional gains in spinal cord injured humans can be achieved through use of treadmill training supplemented by afferent stimulation and adrenergic drugs.

Long-term care of spinal cord injured patients

This is considered in more detail in Chapter 17. Complications of long-term management include pressure sores, autonomic dysreflexia, spasticity, syringomyelia, deep vein thrombosis and respiratory problems. Regular turning and good standards of nursing care, physiotherapy, compression stockings, subcutaneous low molecular weight heparin and antispasmodic medications minimize these risks. Autonomic dysreflexia is an exaggerated response to normally innocuous stimuli, occurring in patients with spinal cord injury above T6, and resulting in tachycardia, hypertensive surges, sweating, anxiety and headache. The most common causes are bladder distension, faecal impaction, urinary tract and other infections, tight clothing and mild pain (pressure sores or ulcers). Treatment involves identifying and eliminating the stimulus, and pharmacological control of blood pressure and anxiety if required.

Prospects for repair of spinal cord injuries

When nerve fibres are severed, as in spinal cord injury, there is an immediate loss of function. Over time, the patient generally recovers some of the loss by re-assigning functions within the surviving undamaged parts of the nervous network, and also by establishing new connections among the surviving parts. However, the nerve fibres that have been severed do not regenerate so the original pattern of connections is never restored. To the extent that the severed fibres carry unique information, the patient endures a permanent and currently incurable functional deficit that cannot be compensated for by reassignments and rearrangements within the surviving network. The purpose of basic research in this field is to provide a basis for clinical procedures that will overturn this grim prognosis and lead to restoration of lost functions.

There are a number of approaches to repairing severed nerve fibres in the brain and spinal cord. They include diminishing the effects of putative inhibitory molecules, providing additional neurotrophic support for damaged nerve fibres, providing anti-inflammatory and/or neuroprotective interventions, or transplantation of stem cells, and these may be referred to in the cited articles and are discussed in brief in this section. Some have reached or nearly reached the level of clinical trials, but none is yet part of accepted practice. This section discusses the approaches that are a major subject of research and clinical effort in brief before focusing on an approach based on repairing the nervous pathway by transplantation of adult cells derived from the olfactory system.

Broadly, research strategies for spinal repair in humans fall into two interrelated categories.

1 *Neurone based.* The first category is directed towards the neurones. It comprises anti-inflammatory and neuroprotective approaches as well as addition of neurotrophic molecules, which could enhance the growth status of axotomized neurones. Included in the category of neurone-orientated repair is the parallel idea of encouraging the formation of new connections (‘sprouting’) that could produce new circuitry to enhance the functional value of surviving undamaged neurones. Another approach to the neuronal defect is the transplantation either of neurones themselves or neural stem cells.

2 *Glia based.* The second category of approaches is directed towards the glia. Attempts to reconstruct damaged glial pathways by transplantation are dealt with later. Another glial-orientated approach is to neutralize the effects of proposed inhibitory molecules present in the glial environment of the spinal cord, thus making the milieu more permissive to axon growth. There are two classes of putative inhibitory molecules. The first includes molecules associated with oligodendrocytic myelin, their receptors and the downstream signalling mechanisms to which they are linked. The second comprises various classes of proteoglycan molecules up-regulated in astrocytic scars and associated with the peri-neuronal net.

Certain general caveats must be borne in mind. The principal symptoms of spinal cord injury are caused by disconnection of ascending and descending tracts of nerve fibres, a large number of whose cells of origin survive. Local destruction of segmental nerve cells at the level of the spinal injury contributes very little to the functional deficits. Therefore, measures to enhance local neuronal survival can only have limited benefit. The same consideration applies to the transplantation either of neurones or of neural stem cells. A number of experiments from different groups have shown that embryonic neurones can be transplanted into adult spinal cord where they survive and establish synaptic connections with the host tissue. However, these transplants have not been found to convey functional improvement.

Proposals for the use of neurotrophic factors are based on the observation that the sprouts of axotomized neurones cease to advance, and that growth-associated molecules become down-regulated. While the principle of adding further neurotrophins could obviously be of value, it has not often been recorded to what extent neurotrophins are in fact absent from the damaged spinal cord. There is also a possibility that further induction of sprouting may also enhance undesirable effects, such as neuropathic pain often associated with spinal cord injury.

In evaluation of the anti-inflammatory measures, it should be borne in mind that the inflammatory response to physical injury is a protective measure whose purpose is not to cause more damage but to enhance tissue healing by encouraging the removal of debris and pathogens and stimulating vascularization. Suppression of the inflammatory response could also impair these processes. The view that inflammation is in itself harmful and increases the size of the original damage is not fully substantiated.

In considering the principle of a molecular approach to the repair of spinal cord injury it is important not to lose sight of the fact that nervous function depends on a complex and accurate pattern of neural connections. Without the restoration of connections the major defects of spinal cord injury cannot be improved. A purely molecular intervention, which does not lead to the reconstruction of pathways, may only be of limited value. It must also be borne in mind that antagonizing molecules that are an intrinsic element of central nervous tissue may have undesirable consequences because of the disturbance of their normal function.

The fact that there are so many different approaches to the repair of injuries to the spinal cord is encouraging, showing the widespread interest in this area, and suggesting many potential candidates for a future therapy. The different approaches are not mutually exclusive, and indeed the idea of combination therapy is becoming current. The remainder of this chapter deals with the concept of repair of glial pathways and its experimental and clinical implications.

Neural plasticity

There are two important observations on the damaged nervous system. The first is that after injury the severed ends of cut nerve fibres, like the stumps of felled trees, send out vigorous, ever-increasing and persistent sprouts (the neuroma). The second is that nerve cells that have been denervated – i.e. deprived of input from one set of fibres – rapidly refill the vacant space (reinnervation) by acquiring new adventitious connections formed opportunistically by adjacent undamaged nerve fibres. These observations indicate that damaged nerve cells retain a persistent vitality, and that they can and do respond positively to injury. This function is referred to as plasticity; it is a function that science is only at the early stages of understanding.

For the patient with brain or spinal cord injuries the existence of plasticity provides a paradox. If severed nerve fibres are able to sprout, and if denervated nerve cells are spontaneously reinnervated by newly formed connections, two important questions arise: first, why do the brain and spinal cord not repair themselves in the same manner, as do other adult tissues such as skin and bone, and, secondly, why are the sprouts produced by the cut nerve fibres unable to cross the gap separating them from their original target destinations, even though those targets are both willing and able to receive new connections to fill the vacant space? These questions focus attention on the nature of the tissue that separates the cut fibre sprouts from their original targets, and how that tissue differs from the original tissue along which those nerve fibres grew during their normal embryonic development. The pathway hypothesis of repair proposes that the failure of regeneration of nerve fibres is because of loss of a suitable pathway.

The pathway hypothesis

The pathway along which nerve fibres travel is made up of at least four types of glial cells arranged in a repeating lattice. Much current interest focuses on the adult glia, astrocytes, whose cell bodies are prolonged into elongated thread-like structures aligned like railway tracks and forming the pathways along which nerve fibres travel. The astroglial cells, which it is thought are key to the events preventing nerve fibres regenerating, react to injury by forming a scar. This scar has the vital function of closing off the injury and restoring the blood–brain barrier needed to protect the nervous system and preserve the sequestered ionic environment that the nervous system requires for its function. At the same time, however, the scarring astrocytic structures set up a massive barrier to the advance of the nerve fibre sprouts produced by the severed nerve fibres.

One of the first approaches to restoring a pathway for severed nerve fibres in the brain and spinal cord was the idea of transplanting a segment of a pathway tissue taken from a part of the body where severed nerve fibres are able to elongate, i.e. the peripheral nerves. Transplanted into areas of damage in the central nervous system, pieces of peripheral nerve ‘picked up’ the sprouts of cut central nerve fibres, whose progress would otherwise be blocked in the astrocytic scar, and provided a conduit that allowed them to elongate for great distances. This effect depends on the presence of living cells in the peripheral nerve grafts, and the same effect could be produced by transplantation of cultured Schwann cells, the unique type of glial cells present in peripheral nerve tissue and absent from the normal brain and spinal cord. Unfortunately, Schwann cell transplants suffered a serious limitation. Although they allowed the growth of nerve fibres out of the damaged brain or spinal cord and into the graft, the fibres remained trapped in the graft and very few were able to leave it and re-enter their original pathways. The astrocytic barrier had been opened for entry but not for exit. It has been discovered that olfactory ensheathing cells, when transplanted, can allow regenerating fibres to leave the astrocytic environment but also allow them to cross back into the astrocytic territory of the damaged spinal cord.

The olfactory system

Until the 1970s it had been thought that no new nerve cells are formed in the adult brain, but with new labelling techniques it was found that in one part of the nervous system – the olfactory system – new nerve cells are being continually generated by division of an adult stem cell located in the nasal mucosa. Throughout normal life, and also at a much accelerated rate after injury to the olfactory nerves, the adult olfactory nerve cells die and are completely replaced by the progeny of adult stem cells lying in the olfactory mucosa. The nerve fibres belonging to the new nerve cells grow through the cribriform plate of the base of the skull and enter the brain. Thus, the glial pathway cells in the olfactory nerves – now called olfactory ensheathing cells (OECs; Plate 15.1 and Figure 15.18) – are capable not only of sustaining long growth of nerve fibres, but they are also able to negotiate an entry through the astrocytic coverings of the surface of the brain even after injury. Can transplantation of OECs provide the glial bridge to allow regeneration?

Animal models

In a rat model of spinal cord injury it was observed that transplantation of cultured adult OECs into complete unilateral lesions of the corticospinal tract resulted in the formation of a

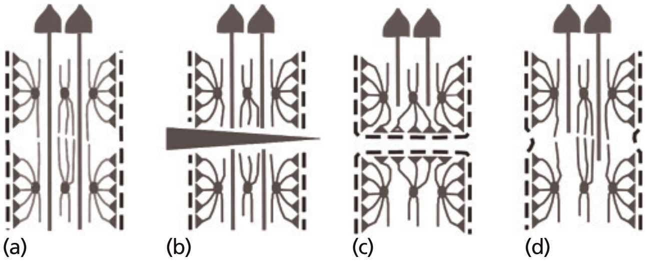


Figure 15.18 Steps in olfactory ensheathing cell (OEC) facilitated spinal regeneration. (a) Intact spinal cord. (b) Sectioned spinal cord. (c) Glial scar formation in sectioned spinal cord. (d) Pathway re-opened following OEC transplantation.

cellular bridge across the defect. The profuse sprouting of the cut ends of the severed nerve fibres was repressed and in their place the cut fibres extended rapidly (at around 1–2 mm/day) as a single long straight process which passed through the transplants and across the astrocytic scar back into the spinal cord (Plate 15.2). Once back in the spinal cord, the regenerating fibres travelled through the distal part of the corticospinal tract to reach an area of their normal target tissue where they regenerated a terminal arborization similar to that of normal corticospinal fibres. The OEC grafts had thus restored a connection that had been severed by the original damage. This repair could be produced by transplantation several months after the original injury, a time when a dense astrocytic scar would already have been formed, thus indicating a powerful reorganizing effect of OECs on astrocytes which had already organized themselves into a scar.

When the OECs were transplanted into complete lesions in animals, which showed permanent loss of function, the anatomical reconstruction of the severed corticospinal pathway was accompanied by return of the ability to learn the directed forepaw reaching task. The putative role of OECs in spinal repair is summarized in Figure 15.18.

Future for clinical application of OEC transplantation

The encouraging reparative results in animal experiments have led to a clinical safety trial in Brisbane, Australia, which has shown no adverse side effects following transplantation of OECs cultured from biopsy samples from the patient's own olfactory mucosa and injected as a suspension at multiple sites in spinal cord injuries. So far, however, functional improvements have not been observed. One possible explanation for this lies in the early stage in development of the cell technology, and the experience serves to illustrate the further work that still needs to be carried out at the research level.

Even with autografts of OECs cultured from biopsy samples of the patient's own nasal mucosa, there remains an urgent need to characterize the human cells and establish a standard culture technology. Although typically located posteriorly on the superior turbinate bone and adjacent lining of the spheno-ethmoidal recess and nasal septum, considerable variability has been reported in the distribution of the human olfactory area and its histology, probably as a result of the inevitable accumulation throughout life of the effects of periodic infectious and allergenic insults, as well as continuous exposure to damaging agents in the environment we have to breathe. It would be helpful to have further characterization of the map of the topographical distribution and the degree of variability that will be encountered in obtaining OECs from small nasal mucosal samples.

Evaluation of OEC transplantation

The problems in evaluating the possible clinical benefits of transplantation of OECs are exacerbated by the natural history of spinal cord injury. The majority of spinal injured patients show a degree of spontaneous recovery, extending over a period of at least 1–2 years, and even of those who on admission have no movement and severe sensory loss, around 40% will recover at least aided walking at the time of discharge. This makes it difficult to be certain of the extent that any intervention, especially in the acute phase, has contributed either positively or negatively to any observed recovery. Claims for the potential contribution of OEC transplants will also have to control for the known major improvements produced by physiotherapy and relearning, as well as any benefits resulting from the other aspects of the surgical interventions. Minimally, a long-term and preferably blind quantitative follow-up of the pre-operative and postoperative symptom history of the spinally injured patient will be needed to provide assurance that benefits are brought about by transplantation of OECs.

To identify a situation that may give a more convincing and rapid answer, we are planning to examine the effects of OEC transplantation in traumatic injuries resulting in avulsion of spinal roots. There have been a number of experimental studies of transplantation of OECs into the dorsal root entry zone of avulsed dorsal roots. Experiments in a repaired lumbar dorsal root in rats show an ingrowth of up to 10% of fibres.

Clinically, avulsion of dorsal roots leads to an immediate and permanent loss of sensation, for which there is no known method of repair. Unlike the spinal cord itself, where transplantation would involve developing novel surgical approaches, surgical access to the spinal roots is already in practice. This, and the ability to bridge large gaps with peripheral nerve grafts, means that the small numbers of OECs that can be obtained, combined with the use of endogenous matrix to retain them, should be sufficient to bridge the gap to the denervated spinal cord. Combined with the positive animal data, a predictable natural history, the availability of a routine surgical approach and the availability of sufficient cells to bridge the gap, make the repair of brachial plexus avulsion an attractive first situation for evaluating the benefits of clinical transplantation of OECs. The first trials of this approach are underway.

Spinal tumours

Spinal tumours may be benign or malignant, primary or secondary. Consideration should always be given to the tissue of origin. Most spinal tumours are metastatic malignant tumours. Breast, bronchus, kidney, prostate, thyroid, multiple myeloma and malignant melanoma are the most common tumours.

Tumours can also be categorized by their anatomical location, i.e. extradural or intradural. Intradural tumours may be extramedullary or intramedullary (Tables 15.7 and 15.8). Intramedullary spinal cord tumours account for approximately 2% of adult and 10% of pediatric central nervous system neoplasms. In adults, 85–90% of intramedullary tumours are astrocytomas or ependymomas. Ependymomas account for approximately 60–70% of all primary spinal cord tumours found in adults, while in children 55–65% of intramedullary spinal cord tumours are astrocytomas. Haemangioblastomas account for 5% of tumours, whereas paragangliomas, oligodendrogliomas and gangliogliomas account for the remainder. Astrocytomas and ependymomas are more common in patients with neurofibromatosis Type 2, which is associated with an abnormality on chromosome 22. Spinal haemangioblastomas occur in 30% of patients with von Hippel–Lindau syndrome, which is associated with an abnormality on chromosome 3.

Clinical presentation is typically with pain and neurological dysfunction. Night pain or pain at rest is typical. Nocturnal pain is related to disturbances in CSF venous outflow causing engorgement and swelling of the spinal cord. Axial spinal pain not located in the lumbosacral region should be regarded as a red flag and warrants further investigation, particularly if it is associated with weight loss, decreased appetite or previous medical history of malignancy.

Investigations include blood tests, urine analysis for Bence-Jones protein, and other tumour markers. Radiologically, plain X-rays, CT, MRI, isotope bone scan, positron emission tomography (PET) scan are all potential imaging technologies. For primary bone tumours it is desirable to have maximal information prior to treatment. A biopsy (Tru Cut or fine needle aspiration under CT scan guidance) can be very helpful in treatment decisions. For example, the prognosis from Ewing's tumour (see below) is better if chemotherapy is given pre-operatively. Similar treatment protocols should be for treatment of osteosarcoma. Other tumours are best dealt with by an en bloc dissection. Identification of tumour type at an early stage is of vital importance in planning definitive treatment.

Pre-operative MRI imaging in many cases allows a pre-operative diagnosis to be made. It is now an essential part of tumour localization and characterization necessary for pre-operative planning. MRI features helpful for diagnosis are shown in Table 15.9.

Spinal manifestations of neurofibromatosis Type 1

Neurofibromatosis is dealt with elsewhere in this book but its spinal manifestations are especially important. These include various tumour types but also varied and complex spinal deformities (kyphoscoliosis) and dural ectasia.

Table 15.7 Classification of intradural intramedullary spinal tumours.

Tumour type	Incidence in adults
Ependymoma	65%
Astrocytoma (pilocytic/fibrillary, WHO I/II)	30–35%
Glioblastoma multiforme (WHO IV)	1.5%
Haemangioblastoma (25% of patients have von Hippel–Lindau)	1–3%
Other glial tumours (oligodendroglioma, ganglioglioma)	Very rare
Metastases	Rare
Cavernomas	Rare

Table 15.8 Classsification of intradural extramedullary tumours.

Meningioma
Neurofibroma/schwannoma including dumb-bell tumours
Paraganglioma
Metastatic including lepromeningeal disease
Arachnoid cyst
Perineural cysts including Tarlov cysts
Epidermoid

Table 15.9 Magnetic resonance imaging characteristics of intradural spinal tumours.

Ependymoma
T1-weighted images – isointense signal with spinal cord
T2-weighted images – hyperintense signal
Strong homogeneous enhancement with contrast

Astrocytoma
T1-weighted images – isointense or hypointense signal with spinal cord
T2-weighted images – hyperintense signal
Cyst formation
Heterogeneous enhancement with contrast

Haemangioblastoma
T1-weighted images – isointense signal to spinal cord
T2-weighted images – hyperintense signal
Cystic with tumour nodule (50–70%)
Enhances strongly with contrast
Extramedullary extension in 15%

Neurofibromas

The typical spinal nerve sheath tumours seen in neurofibromatosis Type 1 (NF1) patients are benign neurofibromas. They consist of fibroblasts, nerve sheaths and nerve cells. The nerve cells are incorporated into the tumour mass, which complicates surgical removal of the tumour. The spinal nerve root neurofibromas in NF1 are often asymptomatic. A rapid increase in size may be a sign of malignant change, albeit a rare complication; less than 5% of NF1 patients develop neurofibrosarcomas. In most instances, malignant progression of the fibroblast component appears to be responsible for the development of malignancy, and molecular genetic studies suggest that inactivation of the p53 tumour suppressor gene is an important factor in the sarcomatous progression of neurofibromas.

Fusiform neurofibromas of spinal nerves are usually bilateral, extend to the branch fibres of the nerve and exceed 30 cm in length. They are seen on CT scans as tumours of low attenuation with areas of higher density, which enhance with intravenous contrast medium. MRI shows nerve sheath tumours to be iso- or slightly hyper-intense with respect to muscle on T1, enhanced T1 and T2 sequences. In approximately 50% of cases, a target pattern with a peripheral hyperintense rim and central low intensity may be seen. This pattern corresponds histologically to peripheral myxomatous tissue and central fibrocollagenous tissue. This pattern is absent in lesions with cystic, haemorrhagic or necrotic changes.

Benign nerve sheath tumours usually have intradural extramedullary location. They extend extradurally and have a dumb-bell configuration through the intervertebral foramen in as many as half of cases. Solitary tumours may involve individual nerves, or multiple nerves may be involved in a plexiform fashion. The tumours are usually multiple, appear at different levels and show different stages of growth. Plexiform neurofibromas involve long segments of the spinal nerves and extend into the spinal cord. They appear more frequently in the second and third decades of life, and the cervical and thoracic segments are primarily affected.

Thakkar *et al.* (1999) studied 54 patients with NF1 aged 5–56 years and found spinal tumours in 65%. A tumour was discovered in almost all symptomatic patients and in 40% of asymptomatic patients. The site of the tumour was intramedullary in 6%, intraspinal extramedullary in 33% and intraforaminal in 57%.

Lesions of the bony spine in NF1

Spinal and skeletal changes are observed in up to 71% of NF1 patients. They can be classified as:

1 Bony erosions caused by a tumour;

2 Pressure damage from intradural, extradural and paravertebral nerve sheath tumours affecting mainly the intervertebral foramen and the spinal canal;

3 Osteomalacia from a genetic tubular defect;

4 Congenital abnormalities, such as macrocranium; and

5 Mesodermal dysplasias, such as pseudoarthrosis of the extremities, local gigantism and scoliosis.

Abnormal spinal curvature is detected in up to 40% of NF1 patients. The majority of cases develop problems between 11 and 16 years of age. A short segment of angular scoliosis with five or fewer vertebrae primarily involved, usually located in the lower thoracic region, may be diagnostic of NF1.

Kyphosis of varying degrees is usually associated with NF1-scoliosis. Kyphosis has been considered a poor prognostic sign because of its tendency to rapid progression and resistance to all types of treatment.

Localized or multi-level dural ectasia with enlargement of the spinal canal is also a relatively common finding in neurofibromatosis and is strongly associated with kyphoscoliosis. On X-ray, dural ectasia is associated with vertebral scalloping or concavity of vertebral bodies.

The cause of dural ectasia may be a congenital weakness of the dura, in which case the constant pulsation of CSF causes progressive enlargement of the dural sac with resultant scalloping of the posterior portions of the vertebral bodies and erosion of the pedicles. Scalloping of bone may also result from NF1-related primary bone dysplasia. The damaged vertebrae result in disorders of spinal alignment and are interestingly not necessarily directly related to an underlying neurofibroma.

Primary bone tumours

These are comparatively rare. They may be benign, e.g. aneurysmal bone cyst, osteoid osteoma, osteoblastoma or malignant. Some tumours occur much more commonly in younger age groups, e.g. aneurysmal bone cyst or Ewing's tumour. Osteosarcoma has a bimodal age distribution affecting young children and older patients, the latter being associated with malignant changes in Paget's disease. The most common tumours are those arising from the bone marrow, particularly multiple myeloma. A more detailed description of these tumours is outside the remit of this book chapter and the reader is referred to Chapter 20 and more dedicated oncology, haematology or orthopaedic textbooks. A working classification is based on tissue origin with tumour types differentiated into bone forming, cartilage forming, giant cell tumours, bone marrow tumours, vascular tumours, other connective tissue tumours, other tumours and tumour-like lesions. The simplified list in Table 15.10 contains examples of each tumour type and is based on the World Health Organization (WHO) classification.

Treatment of spinal tumours

In 1887, Sir Victor Horsley performed the first successful resection of an intradural neoplasm, the diagnosis of which was initially secured by the neurologist Sir William Gowers. This lesion was an intradural extramedullary tumour located outside the spinal cord parenchyma causing compression of the spinal cord.

Intradural tumours are now dealt with by microsurgical excision. This is aided in certain cases by the use of an ultrasonic aspirator where an en bloc excision is not feasible. Spinal cord monitoring using somato-sensory evoked potentials and motor evoked potentials improves the operative safety margin.

Table 15.10 Modified World Health Organization classification of primary skeletal tumours.

Tissue type	Tumour types
Bone	Osteoma (B)
	Osteoid osteoma (B)
	Osteosarcoma – central and peripheral (M)
Cartilage	Chondroma (B)
	Osteochondroma (B)
	Chondrosarcoma (different types) (M)
Giant cell	Osteoblastoma (B)
Bone marrow	Ewing's sarcoma (M)
	Lymphoma (M)
	Myeloma (M)
Vascular	Haemangioma (B)
	Lymphangioma (B)
	Glomus tumour (B)
	Angiosarcoma (M)
Other connective	Fibroma (B)
	Lipoma (B)
	Fibrosarcoma (M)
	Liposarcoma (M)
	Leiomyosarcoma (M)
Other tumours	Neurofibroma (B)
	Neurilemmoma (B)
	Adamantimoma (M)
	Chordoma (M)
Tumour-like	Simple + aneurysmal cysts
	Fibrous dysplasia
	Eosinophilic granuloma

B, benign; M, malignant.

Ependymomas are usually resectable. Primary astrocytomas can occasionally be completely resected. Surgical excision is easier in children than adults. Complications for intramedullary tumours are common with most patients experiencing short-term neurological deterioration. The role of radiotherapy for intramedullary tumours is controversial (Chapter 20). Repeat surgery should probably be considered first for tumour progression. Many of these tumours are slow growing so treatment effects are difficult to judge. In Brotchi's series of 239 patients with low-grade spinal tumours, 5% worsened, 50% stabilized and 40% improved. A patient's neurological function after surgical intervention depends on his or her pre-operative neurological condition. The goal of surgery is to prevent further neurologic dysfunction and to cure the neoplastic condition with complete resection.

Neurofibromas (schwannomas) are relatively easy to remove, with very low morbidity. This is because schwannomas usually arise from the sensory nerve root and the resulting spinal compression is slowly progressive.

Meningiomas arise from the meninges (Plate 15.3), are more common in women and most often affect the thoracic region. Surgical results are generally very good. Operative morbidity most commonly arises from dural defects producing leakage of CSF. Radical excision of the dural origin of the tumour will give the best chance of cure, minimizing the risk of tumour recurrence.

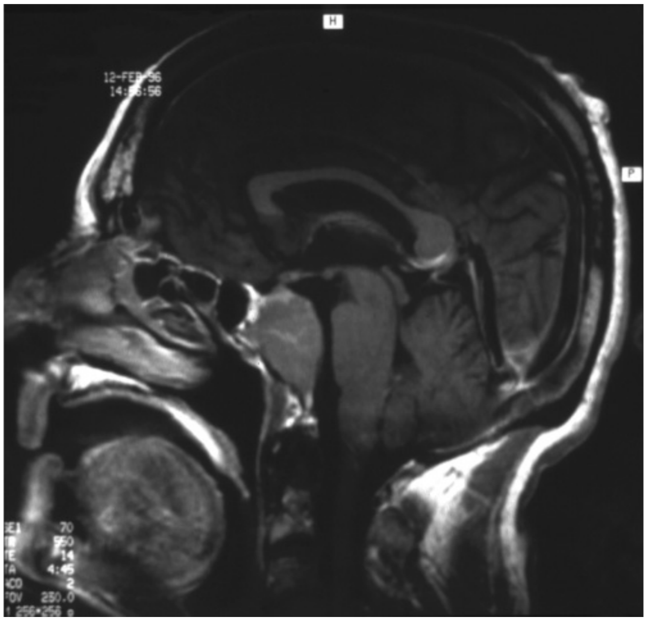


Figure 15.19 Clival chordoma (MRI T1W).

With the exception of Ewing's tumour, primary spine tumours are usually treated by excisional surgery. En bloc resection is useful for chordoma but is often not technically possible. Chordomas arise from the notochord remnants. The majority arise from the most rostral and caudal notochord remnants (craniocervical/clivus and sacral; Figure 15.19).

With the development of more reliable spinal fixation and reconstruction techniques, removal of the whole vertebra is now technically feasible either piecemeal or en bloc. However, in the cervical spine the vertebral artery prevents such an aggressive approach. In the thoracic and lumbar spine posterior en bloc resection is a favoured approach. Titanium mesh expandable cages or stackable carbon fibres cages allow reconstruction of the vertebral body. Spinal stability is also assisted by pedicle screw fixation (Plate 15.4).

Management of metastatic tumours

These are the most common type of spinal tumour (Chapter 20). Historically, surgery involved laminectomy for resection of posterior elements and extradural tumours. While this approach decompressed the spinal cord it further destabilized the spinal column. Most tumours metastasize to the vertebral body and therefore resection of the posterior elements removes the only sound bone in the vertebral complex therefore leading to instability, and deformity with ensuing neurological deterioration and pain. Findlay (1984) found that surgery (laminectomy) provided no better results than radiotherapy alone, and was associated with more complications. However, Patchell *et al.*, in a multi-centre randomized controlled series, have recently demonstrated that surgery and radiotherapy are superior to radiotherapy alone. This study was stopped after planned interim analysis showed superiority of the surgical treatment arm. Outcome measures included pain, ambulation, neurological recovery and bladder control. All outcomes were better with surgical treatment. Other studies have shown surgery should precede radiotherapy. Radiotherapy followed by surgery is associated with a doubling of wound complications such as breakdown or infection.

Degenerative disease of the spine

Cervical spine

Age-related degenerative disease in the cervical spine most commonly affects the mid cervical levels, reflecting the distribution of stress in the neck with upright posture and loading. In younger people, more movement occurs at C5–6 and C6–7 and these levels are the most commonly affected, whereas in older age groups C4–5 and C3–4 become affected in addition. Occasionally, involvement of the atlanto-axial joints and ligaments can produce instability and a soft tissue mass, or 'pseudotumour', in the position of the degenerate odontoid process. Cervical disc degeneration is associated with the formation of osteophytes around the annular attachments to the end-plates, with reciprocal degeneration and hypertrophy of the facet joints. Dehydration of the discs may result in reversal of the normal lordosis to produce a straight neck or even kyphotic deformity. Vertebral subluxations may occur.

Atlanto-axial instability may occur because of degenerative changes in the joints and ligaments at the cranio-cervical junction producing a pseudotumour around the degenerate odontoid process. Treatment involves fusion of C1 and C2, with surveillance MRI to ensure the size of the odontoid mass does not increase. If the diagnosis is in doubt then a transoral biopsy should be taken.

In the subaxial spine, osteophytosis can cause radiculopathy if stenosis of nerve root canals develops, or myelopathy if the spinal canal is sufficiently compromised. Radicular pain usually follows a waxing and waning course, with intermittent exacerbations but, like lumbar radiculopathy, most symptoms of brachalgia settle down with time and surgery is often not required. Surgery may be performed if symptoms fail to improve after 2–3 months, or if neurological signs progress. Surgery to decompress cervical roots may be performed by anterior or posterior approaches. Anterior cervical discectomy with decompression of the nerve roots is performed if there is any coexistent cord compression, or if the majority of root compression is caused by disc prolapse. Posterior foraminotomy is a simpler operation that may be used if there is no cord compression. This approach avoids the small risk of recurrent laryngeal nerve palsy that may occur with anterior operations, and does not require fusion of a motion segment, but is associated with more postoperative neck pain in the short term.

Myelopathy may occur because of disc herniation and osteophytic compression of the cervical cord. Furthermore, the anterior horn cells of the cervical expansion are affected by direct compression, arterial insufficiency, venous congestion, repetitive minor trauma or a combination of these events. In general, 25% of patients with spondylotic cervical cord compression remain static, but 75% progressively deteriorate. It is common to observe an initial deterioration followed by a period of stabilization, but most patients will later progress further if untreated. The main aim of surgery is to prevent deterioration; however, improvement can occur. Surgical treatment may be performed anteriorly, by cervical discectomy and sometimes corpectomy, or posteriorly by laminectomy or laminoplasty. The method of decompression depends on the degree of lordosis or kyphosis of the spine, the main cause of the cord compression and surgeon's preference. If the cord compression is mainly caused by a disc prolapse in a kyphotic neck, then anterior decompression is preferable. Compression from hypertrophy of the ligamentum flavum in a lordotic neck is best treated by posterior decompression. After laminectomy there is a risk of progressive kyphosis because of removal of the posterior tension-band elements of the cervical spine, leading many surgeons to adopt the technique of spinal canal augmentation by laminoplasty which was originally developed in Japan for treatment of patients with ossification of the posterior longitudinal ligament.

The overall results of anterior and posterior decompressive surgery for myelopathy are similar, although it should be remembered that the indications for each approach are different and therefore not directly comparable. After laminectomy in one series, 56% of patients improved, 25% were unchanged and 19% slightly worse, and with anterior decompression 75% of patients improved.

The Smith–Robinson and Cloward techniques for anterior cervical discectomy were originally described with the insertion of an iliac crest bone graft to produce fusion. Some surgeons have since advocated discectomy without fusion, although there is an increased incidence of kyphotic deformity and transient radicular pain after the operation if no graft or spacer is used, because of partial subsidence of the adjacent vertebral bodies and consequent narrowing of the intervertebral foramina. More recently, artificial titanium, plastic or carbon fibre cages have been developed which can be filled with bone and inserted in place of iliac bone graft. The use of cages can decrease the length of operations and avoid complications associated with iliac crest harvest, including pain, infection, haematoma, and even pelvic fracture.

Fusion after cervical discectomy has been the standard treatment for a number of years, but there is an increased incidence of accelerated degenerative disease in adjacent discs, because of the added mechanical stresses placed on adjacent discs after fusion of a previously mobile segment. Within 10 years of fusion, around 29% of adjacent discs will degenerate and require surgery. To avoid this complication, a number of different artificial disc

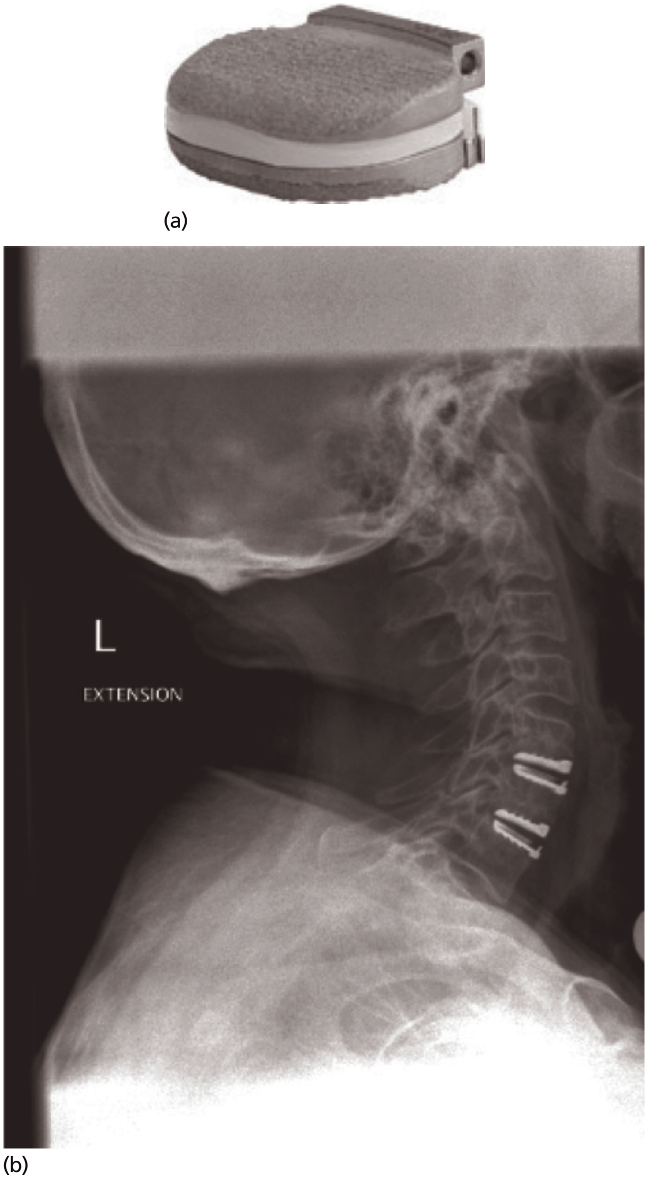


Figure 15.20 (a) Photograph of artificial cervical disc implant. (b) Lateral cervical spine X-ray showing artificial disc implants at two levels.

implants have been developed that do not restrict movement after anterior decompression, and thereby minimize the development of adjacent segment disease (Figure 15.20). The short-term results of artificial disc implants have been favourable, but in the longer term it is unclear whether they will require replacement within a lifetime.

Thoracic spine

Degenerative disease in the thoracic spine is less common than in the cervical and lumbar spine because of the decreased movement that occurs at thoracic levels. Thoracic disc prolapses account for only 0.5% of all disc prolapses and usually occur in younger age groups (third to fifth decades) at T8–12 levels. Patients often present with a history of chronic pain with only subtle sensory or motor changes.

In symptomatic patients, discectomy is performed by an anterolateral approach, most commonly by thoracotomy. Direct posterior approaches are associated with a high risk of mechanical cord damage and should be avoided, although in some cases a postero-lateral approach (transpedicular or costotransversectomy) may be appropriate. The spinal fusion is achieved in a similar way to cervical spine surgery.

Lumbar spine

Lumbar canal stenosis may occur because of acquired degenerative changes such as hypertrophy of facet joints, ligamentum flavum, disc prolapse or spondylolisthesis, or congenital causes such as achondroplasia. If the spinal canal cross-sectional area diminishes below a critical value then radicular symptoms or neurogenic claudication may occur, either because of direct compression or ischaemia of nerve roots. Neurological examination may be normal, including straight-leg raising. The natural history if untreated is a slowly progressive course with most symptoms remaining the same, or gradually worsening over the next few years after diagnosis. Treatment is by laminectomy with or without discectomy; 60–80% of claudication improves after surgery.

Lumbar disc prolapse is a common cause of radicular leg pain, and is present in 1–3% of people with lower back pain. Approximately 80–90% of patients with radicular leg pain improve over the following few months without surgery. Long periods of immobilization should be discouraged and gentle mobilization and exercise can aid recovery. 'Red flags' of urinary incontinence, urinary retention, faecal incontinence, peri-anal numbness and leg weakness should prompt urgent referral for MR imaging to exclude a central disc prolapse and cauda equina compression. Otherwise, unless the pain is refractory to medical treatment, 2–3 months of pain management is recommended before consideration of surgery.

The L4–5 and L5–S1 vertebral discs are the most common levels of disc prolapse. They produce L5 and S1 radiculopathies, respectively. A disc prolapse more commonly involves the nerve root of the level below. For example, at L4–5, although the L4 nerve root exits at that level, it has already exited lateral to the common position of a disc bulge and will not be caught by it unless the bulge is more laterally placed. Instead, the L4–5 disc bulge will usually catch the L5 nerve root *en passant*.

Lumbar microdiscectomy is the standard surgical technique for removing disc prolapses, although percutaneous techniques (using laser, thermocoagulation, chymopapain or mechanical disruption with a nucleotome) and minimally invasive techniques are now sometimes used with varying efficacy. In a randomized controlled trial of microdiscectomy versus non-surgical therapies, surgically treated patients had better outcomes at 1 year, but the difference was not significant by 4 and 10 years.

Low back pain

Low back pain affects 70–85% of population at some point in their lives, with an incidence of 15% and point prevalence of 30%. The primary risk factor is age-related degenerative change in the lumbar spine. The intervertebral discs in particular show degeneration which can be appreciated as loss of hydration on MRI. By the age of 50 years 90% of the population show loss of hydration of the nucleus pulposus.

The disc comprises the nucleus pulposus, a gelatinous structure surrounded by the annulus fibrosus. With ageing there are changes in the collagen matrix, loss of hydration, apoptosis and loss of the blood supply. The hydrostatic mechanisms for dissipation of force are lost. This, coupled with weakening of the annulus, leads to an increased risk of rupture of the nucleus pulposus through the annulus fibrosus. This is most likely to occur during loading of the spine in flexion and torsion. Importantly, the nucleus pulposus is likely to be an immune privileged site like the testis. The evidence for this is that like other immune privileged tissues it expresses the FAS ligand, which induces apoptosis of FAS-positive invading T cells. The annulus fibrosus and notochord elements do not express FAS ligand. Extrusion of the disc into the epidural space sets up an intense inflammatory process with autoimmune reaction and inflammatory cell infiltration. There is a resulting increase in inflammatory cytokines especially interleukin 1, tumour necrosis factor α (TNFα), interleukin 6 along with increased levels of prostaglandin E2. In degenerate discs there is an increase in matrix metalloproteinases (MMPs). MMPs are zinc-dependent enzymes that are involved in modelling of connective tissue. Experimental data implicates MMPs 1 and 2 in the pathogenesis of disc herniation. Ultimately, spontaneous resorption of herniated disc material may occur as the result of action of MMPs and cytokines.

The pain in degenerative spinal disease results from a variety of interacting mechanisms. A major contributor to the pain is the inflammatory response evoked by the disc herniation. There are important nociceptive contributions from the facet joints, vertebrae, muscles, ligaments and fascia. Nociceptive pathways involve the sinovertebral nerve, which arises from the ventral root and grey rami near the dorsal root ganglion to innervate a number of structures, particularly the posterior longitudinal ligament. There is also a noiceptive contribution from the dorsal root ganglion.

Management of lower back pain

Pain may be managed by conservative and surgical methods. If radicular pain is very severe, then bed rest may be advised to minimize loading of the lumbar spine and nerve root foramina, with analgesia (including paracetamol and non-steroid anti-inflammatory drugs), and sometimes benzodiazepine muscle relaxants. However, prolonged bed rest beyond 3–4 days should be discouraged because it is usually associated with a worse outcome than a gradual return to normal activities and work. Heavy lifting, prolonged sitting and abnormal postures should be discouraged, and a program of gentle exercise and education established, often supplemented with physiotherapy. Correct posture, sleeping position and lifting techniques are important.

Chiropractic and osteopathy, acupuncture, epidural steroid and facet joint injections may help in the short term, but there is little evidence of long-term benefits. Spinal manipulation should not be performed in the presence of severe or progressive neurological deficit.

Surgical lumbar fusion is accepted practice in the presence of instability resulting from tumour, trauma, infection or degenerative disease, but its use for mechanical back pain alone is controversial. A randomized controlled trial comparing surgical fusion with an intensive rehabilitation programme revealed improvements in both groups after treatment, but no significant difference between surgery and rehabilitation. Whereas surgical fixation was associated with an improved outcome, there is limited evidence to support the use of surgery in the absence of instability. In fact, surgical fusion of a mobile segment is associated with exaggerated adjacent disc disease in 20% of patients over the next 10 years after surgery. This has stimulated interest in artificial disc replacements, such as the 'ProDisc' and 'Charite' prosthetic lumbar discs, which have been associated with good outcomes in back pain and patient satisfaction after 2 years from operation. However, recent reports may suggest that some of these disc replacements actually result in a fusion anyway, without changing the patient outcome.

Spinal infections

All components of the spine are vulnerable to attack by bacterial, fungal, viral and parasitical infections. The structures involved include the vertebral column, most commonly the intervertebral disc (discitis) and the vertebra (osteomyelitis). Infection can spread to the extradural space with abscess formation and the intradural contents can also be affected. Intramedullary infection is very rare. Further detailed discussion of infectious disease of the nervous system and spine can be found in Chapter 8.

Bacterial infections

In adults, lumbar bacterial infections often originate from urinary tract infections which drain via the Batson venous plexus. The respiratory system is a common source of blood-borne infection with spinal infection usually following the initial infection by some 1–8 weeks. Purulent material may break out of cortex of the bone anteriorly to form a paravertebral abscess or posteriorly to form an epidural abscess. Infection-related weakening of the bone may cause vertebral body collapse. Haematogenous osteomyelitis is seen more often in children than adults. This is believed to be because the epiphyseal plate site present in the growing skeleton of a child and absent in adults is more vulnerable than mature bone to blood-borne infection. Risk factors for bacterial spinal infection include an immunocompromised state, including diabetes, TB, HIV, malnutrition and intravenous drug use.

The risk factors for bacterial discitis are the same as those for osteomyelitis. Iatrogenic cases occur after disc surgery, therapeutic injections, lumbar puncture and epidural anaesthesia. The most common organism is *Staphylococcus aureus*, particularly *Staphylococcus epidermidis*. Methicillin-resistant *Staphylococcus aureus* (MRSA) can occur. *Streptococcus viridans* is the next most common infecting organism.

Blood cultures sometimes identify the infecting organism and guide appropriate antibiotics use. Because of difficulty in obtaining a culture from blood, CT-guided biopsy of the infected area should always be considered prior to antibiotics. Epidural abscesses are usually considered to be a surgical problem but in a debilitated patient with a small thin abscess and a bacteriological diagnosis, appropriate antibiotic therapy alone is a reasonable approach.

Antibiotics are given for variable lengths of time and 2–3 months of parenteral antibiotic therapy may be required. Before parenteral antibiotics are discontinued, the erythrocyte sedimentation rate (ESR) should have fallen to at least two-thirds of the pre-treatment level. In addition, the patient should be afebrile, without pain on mobilization, and ideally improving from disease-related neurological complications. A persistently high ESR or C-reactive protein implies continuing infection, and additional intravenous antibiotics are indicated. In such an instance, additional biopsies for microbial culture may need to be taken.

Bracing or other forms of orthosis is strongly recommended to provide stability for the spine while the infection is being treated and the tissues are healing. The goal of spinal immobilization is to provide opportunity for the affected spinal level(s) to fuse in an anatomically aligned position. Bracing is usually continued for 6–12 weeks, until either a bony fusion is seen on radiography or until the patient's pain subsides. A rigid brace is optimal and only need be worn when the patient is upright or mobile.

Spinal tuberculosis

Mycobacterium tuberculosis of the spine is an uncommon form of tuberculosis occurring in less than 1% of patients with tuberculosis. TB typically first affects the intervertebral discs. The primary risk factors for TB infection in the UK include membership of an ethnic group in which the disease is endemic and/or being in an immunocompromised state.

TB infection typically presents with local pain, fever, night sweats and general ill health including weight loss. If the disease spreads from the disc into the vertebral body osteomyelitis will occur with epidural abscess formation and/or vertebral body collapse. Pathological fractures will cause pain, deformity (kyphosis) and in some cases spinal cord compression.

The diagnosis is difficult in patients with no evidence of extraspinal TB. The clinical presentation together with the radiological appearances (plain X-ray, CT and MRI) of spinal TB and a positive tuberculin test usually suggest a diagnosis of spinal tuberculosis (Figure 15.21).

In Pott's disease, the spinal cord may become involved either because of compression by disrupted bone and/or disc and ligaments, expansion of a TB abscess or by direct invasion of cord and leptomeninges by granulation tissue. Primary tuberculoma of the spinal cord is rare. Neurological deficits when present usually develop gradually. A positive diagnosis is made from detection and culture of acid-fast bacilli from the bone or body fluids. Polymerase chain reaction (PCR) detection of mycobacterium DNA may speed the diagnosis but initiation of effective treatment should not be delayed if the clinical index of suspicion is high.

With the advent of effective combination chemotherapy in the early 1950s, the mortality rate among patients with spinal TB decreased from nearly 100% to 3%. It is important to note that while triple and quadruple therapy drug regimens remain highly effective for most cases of spinal TB, in immuno-compromised patients, especially those with HIV/AIDs, drug-resistant TB is an increasing problem.

Management of spinal TB and the role of surgery

The initial procedure introduced for the surgical treatment of spinal infections was laminectomy. However, this procedure did not allow access to anterior abscesses and contributed to spinal instability, which often resulted in progressive deformity. Hodgson and Stock (1960) extensively reported this procedure in the treatment of TB of the spine. Late spinal deformity was prevented with spinal fusion and instrumentation. The need for an anterior approach (by thoracotomy) was stimulated by the failures of posterior fusion in some of their patients, many of whom had TB involving four to eight vertebrae and such pronounced kyphosis as to make posterior fusion mechanically unsound. The current surgical management of spinal TB requires of radical debridement and anterior fusion. The anterior approach gives a wide access to the disease. The removal of all avascular bone is essential to ensure rapid sound bone fusion. Anterior fusion by bone transplantation after a thorough excision of the disease focus is successful in a very high proportion of cases.

The Medical Research Council (MRC) examined the role of surgery for spinal TB with antibiotic chemotherapy versus antibiotic chemotherapy alone. The first MRC trial of the treatment of spinal TB revealed equivocal results at 5 years when chemotherapy alone was compared with radical surgical treatment combined with chemotherapy (MRC working party on TB of the spine, 1974). The primary advantage of anterior spinal arthrodesis was a decreased tendency for progression of deformity. The role of surgery for spinal TB has been re-examined in a recent Cochrane review. This concluded that the data were insufficient to be clear whether surgery with chemotherapy is better than chemotherapy alone. However, it is very important to note that very few patients in the MRC trial were neurologically affected. Furthermore, it is important to appreciate that the surgical approach analysed by the original MRC trials is not comparable to modern spinal surgery performed by specialist spinal surgeons with high-quality spinal instrumentation, modern

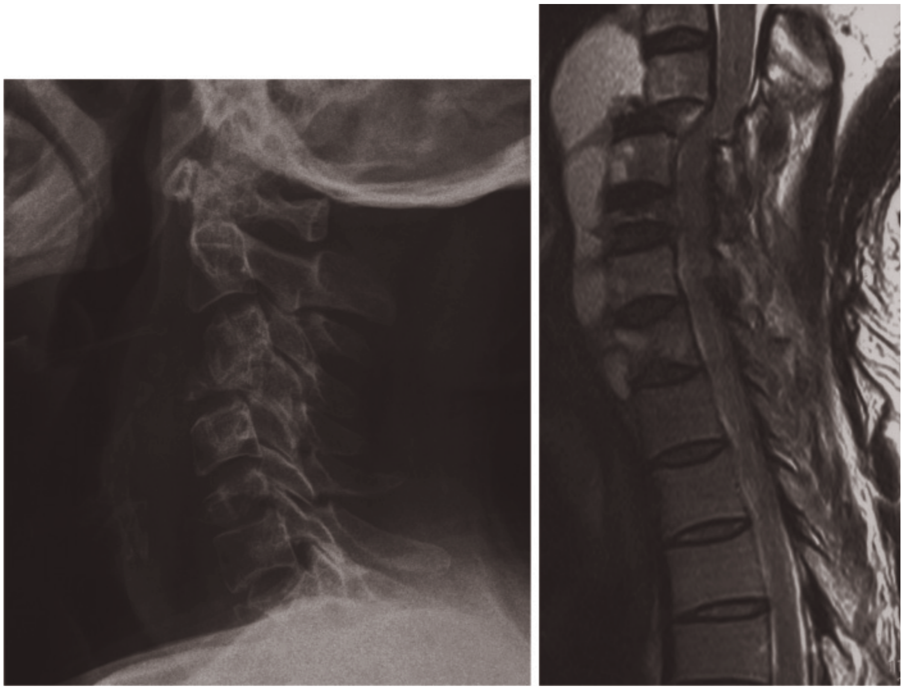


Figure 15.21 Spinal TB. (a) Pathological collapse C3/4 disc space and C6 vertebra with retropharyngeal swelling (lateral X-ray). (b) Pre-vertebral swelling, kyphosis and cord compression (MRI T2W).

anaesthesia, intra-operative neurophysiological monitoring with decisions informed by neurologists and infectious diseases specialists and by modern radiology (MRI and CT). Surgery may be indicated in certain subgroups of patients, particularly those presenting with a significant neurological deficit, with progressive neurological deficits, those who develop neurological deficits on appropriate antibiotic therapy and those with an initial kyphosis angle greater than 30°, especially if a child with further skeletal growth potential.

Fungal infections

Fungal infections of the spine are rare. Fungi such as *Cryptococcus*, *Candida* and *Aspergillus* are found worldwide, whereas *Coccidioides immitis* and *Blastomyces dermatitidis* are limited to specific geographical areas. *Aspergillus* and many *Candida* species are normal commensals of the body and produce disease in susceptible individuals when they gain access to the vascular system through intravenous lines, during implantation of prosthetic devices or during surgery. Other fungi produce spinal involvement usually as a result of haematogenous or direct spread of organisms from an initial pulmonary source of infection. Involvement of the vertebral bodies can lead to vertebral compression fractures and gross deformity of the spine. Spread of infection along the anterior longitudinal ligament can lead to psoas or paravertebral abscesses, similar to tuberculosis. Recognition of the disease requires a high index of suspicion, proper travel history and a detailed physical examination. Treatment relies on the early and effective pharmacotherapy and constant monitoring of clinical progress. Resistance to medical therapy, spinal instability and neurologic deficits are indications for spinal debridement and stabilization with spinal fusion. Prognosis depends on the premorbid state of the patient, the type of fungal organism and the timing of treatment. Immuno-compromised patients fare badly.

Viral infections

Tropical spastic paraparesis (TSP) is an incurable viral infection of the spinal cord that causes weakness in the legs. It is caused by the human T-cell lymphotropic virus-1 (HTLV-1) retrovirus. Symptoms may begin years after infection. In response to the infection, the body's immune response may injure nerve tissue, causing symptoms that include neurogenic bladder problems, leg pain and loss of feeling in the feet, tingling sensations and unpleasant sensations when the skin is touched. Patients with TSP may also exhibit uveitis, arthritis, pulmonary lymphocytic alveolitis, polymyositis, keratoconjunctivitis sicca and infectious dermatitis. Factors that may have a role in transmitting the disorder include being a recipient of transfusion blood products (especially before 1989), breast milk feeding from a seropositive mother, intravenous drug use or being the sexual partner of a seropositive individual for several years. Not every HTLV-1 seropositive carrier will develop TSP; fewer than 5% will exhibit neurological dysfunction or, eventually, haematological malignancy such as adult T-cell leukaemia/lymphoma.

Treatment of tropical spastic paraparesis

Initial trials of treatment using antiretroviral drugs have not produced neurological improvement nor have they convincingly shown a slowing of disease progression. Essentially there are two approaches. The first is to try to inhibit viral replication. This has been attempted with antiviral drugs: the reverse transcriptase inhibitor zidovudine (AZT) and the cytosine analogue lamivudine alone and in combination. Problematically for this approach, in contrast to HIV, the virus replicates without the need for reverse transcription. These drugs can produce a reduction in HTLV1 pro-viral load. However, little clinical response was seen in a randomized double-blind placebo controlled trial of Combivir (zidovudine + lamivudine). The second approach has been to suppress the immune response both with steroids and steroid-sparing drugs and interferon-1α. Although short-term improvements have been noted no sustained clinical improvement or measurable reduction in disease progression is yet reported in rigorous analysis of the effects of these approaches. Future trials are in progress and are planned to assess the affects of ciclosporin, anti-TNFα and Campath 1H.

There are numerous viral causes of transverse myelitis which are discussed in the following section and in Chapters 8 and 10.

Spinal cord inflammation

Devic's disease (neuromyelitis optica)

The evidence is now strongly that this disease is a separate entity from multiple sclerosis (MS). It is characterized by episodes of myelopathy (Figure 15.22) and optic neuropathy which are often severe. It is more common amongst the Japanese. The involvement of optic nerve and spinal cord is selective. The condition is also discussed in Chapter 10.

A Devic-like syndrome is also described in association with other autoimmune diseases including systemic lupus erythematosus (SLE). Neurological sarcoidosis may also present with a Devic-like picture of spinal and optic nerve inflammation. Devic's disease is in the differential diagnosis of paraneoplastic syndromes and spinal cord infections. In these conditions there is a myelitis sometimes associated with optic neuropathy. Often an extensive investigation is required to look for evidence of SLE, sarcoid and neoplasia. The differential diagnosis of transverse myelitis is very extensive (Table 15.11). However, if the NMO-IgG serum test proves to be clinically useful then such extensive investigation to search for diseases driving Devic-like myelitis and optic neuritis may be unnecessary.

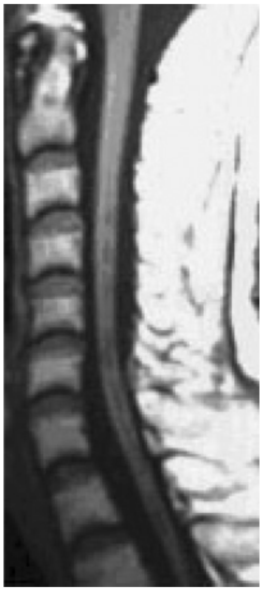


Figure 15.22 Devic's disease: extensive intrinsic cord lesion with cavitation (MRI T1W).

Table 15.11 Causes of transverse myelitis.

Infections	Bacterial	Especially staphylococcus, including epidural abscess
		Mycoplasma
		TB
		Borrelia
		Rickettsia
		Syphilis
		Tetanus
	Viral	Enterovirus – coxsackie, poliovius, enterovirus 71
		Flavivirus – West Nile
		HZV, HSV 1, 2
		HIV, HTLV-1
		CMV, EBV
		Influenza
	Parasitic	Schistosomiasis
		Toxoplasma
		Malaria
		Cysticercosis
	Fungal	

Continued on p. 620

Table 15.11 *Continued*

Post-infectious	Acute disseminated encephalomyelitis
Post-vaccination	Especially rabies vaccine, (numerous other case reports)
Primary demyelination	Multiple sclerosis
	Devic's disease
Inflammatory disorders	Systemic lupus erythematosus
	Mixed connective tissue disease
	Sjögren's disease
	Scleroderma
	Rheumatoid disease
	Antiphospholipid syndrome
	Sarcoidosis
	Vasculitides
	Ulcerative colitis
	Behçet's disease
	Serum sickness
	Post-haematopoietic stem cell infusion
	Graft versus host disease
	Immune dysregulation and immune reconstitution in AIDS
Primary neoplasia	Gliomas
	Ependymomas (see above)
Secondary neoplasia	Especially lymphomas, metastases
Paraneoplastic	Especially associated with small cell carcinoma of lung, and lymphoma
Drugs	Heroin
Vitamin deficiency/ toxins; see also Chapter 18	Subacute combined degeneration of the cord (typically B_{12} deficiency; exceptionally copper deficiency)
	Snake and spider bite
	Arsenic
	Diethylene glycol
	Nitrous oxide
	Cynanide
	Intrathecal chemotherapy
Radiation	Dose-dependent, acute, early- and late-delayed
Miscellaneous	Decompression sickness
	Electrical injury

Vascular disorders of the spine

Clinical features

Vascular diseases including those of the spinal cord are discussed further in Chapters 4 and 25. Like vascular disease of the brain the syndromes can be thought of in terms of infarction, haemorrhage, transient loss of vascular supply and vascular malformations.

The clinical manifestations differ between each of the above categories. Spinal cord infarction usually presents acutely, often with pain followed by paralysis and sensory loss. The most common arterial territory involved is the anterior spinal artery. In anterior spinal artery occlusion the anterior two-thirds of the spinal cord is affected. The spinal level is determined by where in its course the supply from the anterior spinal artery is interrupted. The patient presents with an acute flaccid paraparesis with loss of sphincter control and anaesthesia to temperature and pain but classically with preservation of posterior column functions of joint position and vibration sense. The most typical level is the upper thoracic cord but involvement of the cervical spine and even the caudal brainstem can occur. Anterior spinal artery infarction can be partial. The syndromes of posterior spinal artery infarction, watershed infarction, venous infection, transverse infarction, central cord infarction and lacunar infarction are far more rare. Watershed infarcts and spinal artery hypoperfusion causing spinal TIA and 'claudication' may occur because of atheromatous disease of the aorta and its branches. The most common site of hypoperfusion syndromes is the mid thoracic area T4–9 where perfusion is relatively poor. The artery of Adamkiewicz (approximately T6 level) supplies blood to the spinal cord in this region. Common causes of spinal cord infarction are listed in Table 15.12.

Haemorrhage in the spine is classified according to the spinal level and anatomical site. Haemorrhages may be intramedullary, subarachnoid, epidural and subdural. The presentation is usually

Table 15.12 Causes of spinal cord infarction.

Atherosclerosis	Diabetes, hypertension, hyperlipidaemia
Inflammatory	Sarcoidosis, arachnoiditis
Infective	Syphillis, TB, herpes zoster, HIV, bacterial meningitis
Vasculitis	SLE, giant cell arteritis, polyarteritis
Aortic disease	Dissecting aortic aneurysm, aortic occlusion, trauma, Takayasu's disease
Arteriopathy	Connective tissue disease, Marfan's syndrome, fibromuscular dysplasia
Embolic disease	Cardiac embolism, decompression sickness
Hypoperfusion states	Cardiac arrest, hypovolemia, cardiopulmonary bypass
Vertebral artery disease	Dissections, trauma
Hypercoagulable states	Clotting factor disorders, antiphospholipid antibodies, blood transfusion
Drug abuse	Cocaine, heroin, ecstasy
Miscellaneous medical	Anaemia, sickle cell, Moyamoya, CADASIL, Paget's disease
Iatrogenic	Vascular surgery, cardiac surgery, spinal surgery, diagnostic catheter radiology, interventional radiology, spinal/epidural anaesthesia; intrathecal drugs

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy; SLE, systemic lupus erythematosus; TB, tuberculosis.

acute with severe spinal pain and myelopathy with a motor and sensory level and sphincter loss. Spinal subarachnoid haemorrhage presents with severe back pain, radicular pain followed by the classic signs and symptoms of subarachnoid bleeding, i.e. obtundation, neck stiffness and photophobia. Myelopathy may be present but unlike other causes of spinal haemorrhage not necessarily severe.

Vascular malformations

Spinal vascular malformations usually present subacutely unless there is acute haemorrhage (this does not happen with dural AVMs or fistulae). Dural fistulae present as a myelopathy with progressive motor sensory and sphincteric loss. There may be radicular involvement and lower motor neurone signs because of impairment of dorsal and ventral root blood supply as well as anterior horn cell loss. Intradural fistulae more typically present acutely with the affects of intramedullary or subarachnoid bleeding. Adhesive arachnoiditis of the spine may be a late complication of spinal haemorrhage but rarely is a presenting feature leading to the diagnosis of a vascular malformation that has bled previously. Cavernous malformations may present acutely with large intramedullary haemorrhage or with a subacute myelopathy resulting from venous bleeding and consequent spinal damage. The presentation of cavernomas is often with stepwise neurological deterioration.

Neoplastic vascular lesions

Cavernous angiomas (also known as cavernomas, cavernous haemangiomas or malformations) consist of a mass of endothelial cells which form sinusoidal spaces filled with blood, without intervening parenchyma, surrounded by haemosiderin-stained spinal parenchyma. They may present with focal haemorrhage or with mass effect and spinal cord syndromes. Symptomatic cavernous angiomas should be treated by surgical excision to prevent further haemorrhage and progression of deficits, whereas asymptomatic lesions should be observed because the natural history of these lesions is unclear. Definitive treatment should take into account the accessibility of the lesion, age of the patient and degree of neurological deficit.

Haemangioblastomas are neoplastic masses consisting of endothelial cells, pericytes and stromal cells. They may occur sporadically, or as part of von Hippel–Lindau syndrome. They usually are intramedullary, but have contact with the pial surface, and may have an associated cystic component or syrinx. Prior to surgery it is important to localize angiographically the large feeding vessels supplying the tumour, to minimize bleeding during resection. Treatment is by surgical resection, staying on the tumour capsule and dividing feeding vessels as they are exposed, similar to the technique of AVM resection.

Arteriovenous malformations

AVMs account for about 4% of primary intraspinal masses, and may be classified into the following four types.

1 *Type I.* Dural arteriovenous fistulas (AVFs) are the most common type of AVM. AVFs do not have a nidus of abnormal vessels like classic AVMs. Instead, there is a direct connection between an artery and vein, with either single or multiple feeders. The dural fistula is in the root sleeve at an intervertebral foramen, feeding directly into spinal draining veins which may be intradural or extradural (Figures 15.23 and 15.24). They usually present with progressive myelopathy in middle-aged adults, resulting from venous congestion and hypoperfusion of the spinal cord, and are more common in the thoracic spine. Treatment of AVFs involves occlusion of the fistula by surgery or embolization by interventional radiology.

2 *Type II.* Glomus AVMs consist of a nidus of compacted abnormal arteries and veins within the spinal cord which may be fed by multiple normal vessels, such as the anterior and posterior spinal arteries (Figure 15.25). The abnormal vessels are intramedullary, and are similar to the vessels seen in intracranial AVMs,

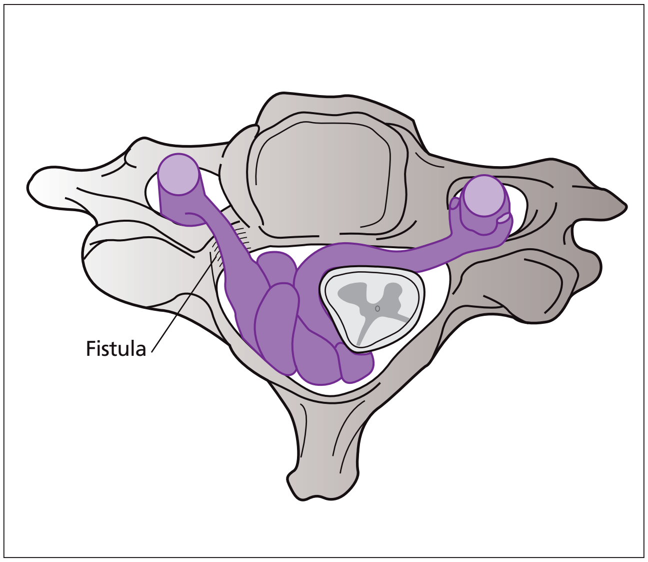


Figure 15.23 Extradural spinal arteriovenous fistula, Type I.

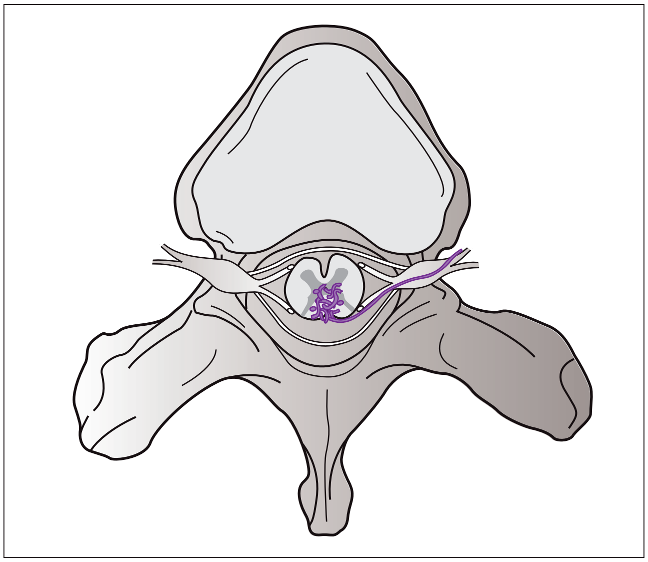


Figure 15.25 Glomus or nidus spinal arteriovenous malformation, Type II.

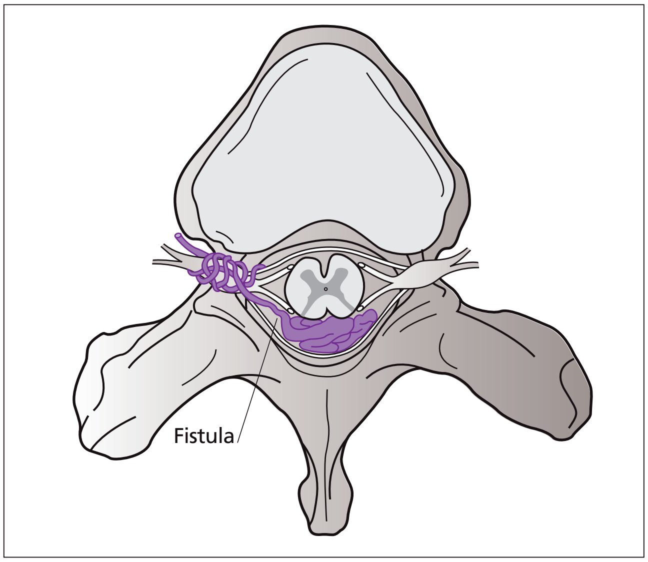


Figure 15.24 Intradural spinal arteriovenous fistula, Type I.

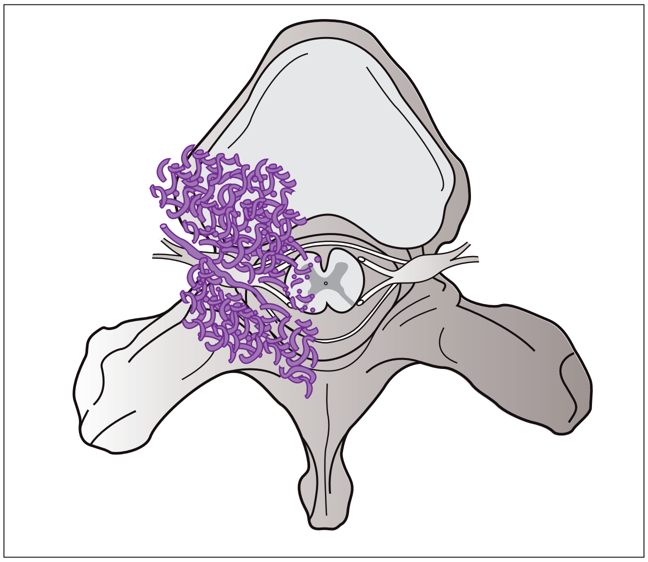


Figure 15.26 Juvenile-type arteriovenous malformation, Type III.

either in a compact mass or diffusely arranged. The vessels in the nidus are usually high flow, resulting in myelopathy from the mass effect or steal phenomena. Treatment is by surgical excision of the nidus, embolization, or both.

3 *Type III.* Juvenile or metameric AVMs are large AVMs that are intradural and extradural, fed by multiple vessels, often involving neighbouring bone and soft tissues (Figure 15.26). They are very difficult to treat and require a multi-modal approach.

4 *Type IV.* These are AVFs on the surface of the cord that are intradural but extramedullary.

Most AVMs present with a progressive neurological deficit over months to years as a result of venous congestion or arterial steal, but may also present with sudden parenchymal haemorrhage, subarachnoid haemorrhage, mass effect or cord infarction. A spinal AVM is an important differential diagnosis for patients with apparent intracranial subarachnoid haemorrhage and normal intracranial angiography, especially when neck stiffness and pain is more of a feature than headache. MRI and spinal angiography are the investigations of choice for diagnosis and treatment planning.

Diagnosis of spinal vascular disease

The differential diagnosis of spinal cord vascular diseases is influenced primarily by the rapidity of symptom presentation. Severe infectious, para-infectious and inflammatory myelitis including Devic's disease may present acutely. However, hyperacute presentations are more suggestive of vascular disease. Subacute and chronic presentations, either without haemorrhage as in dural AVMs or with small venous haemorrhage as with cavernomas, need to be differentiated from the causes of progressive myelopathy, particularly structural causes and spinal demyelination.

MRI is the primary diagnostic investigation. Spinal MRI will detect over 90% of acute spinal cord ischaemic lesions. Diffusion-weighted and contrast-enhanced MRI may increase the yield further. MRI usually excludes compressive lesions and often will find evidence of demyelination especially if cranial MRI is also performed. Imaging of the aorta with abdominal CT, and with CT or MR angiography is important. Subdural and epidural haematomas are detectable but need to be distinguished from abscesses and other causes of fluid collection. AVMs and dural fistulae are usually detectable with expert neuroradiological interpretation of T1.5 MRI. The vessels of the malformation are seen as serpiginous flow voids. In addition, there is usually T2-weighted signal change within the spinal cord substance. However, AVMs and dural fistulae can be missed on MRI. Spinal myelography has detected the vessels of AVMs and dural fistulae that are not visible on MRI. Finally, spinal angiography may be required both for definitive diagnosis and to plan treatment with interventional radiological occlusion either through embolization or gluing techniques.

In suspected spinal subarachnoid haemorrhage cranial CT often detects subarachnoid blood and a lumbar puncture will provide definitive evidence of subarachnoid haemorrhage. Other investigations are directed towards detection of the cause or contributing factors of the infarct or haemorrhage (e.g. looking for infections such as syphilis, hypercoagulant and hypocoagulant states and vasculitis).

Management of spinal vascular disease

There is no curative treatment for acute spinal cord infarction. During high-risk vascular procedures pre-treatment with steroids and opiate antagonists has been advocated and neuroprotective agents have been examined in the basic science setting. However, there is no clinical evidence for effectiveness of any of these approaches. Some vascular surgeons advocate spinal fluid drainage during surgery believing that through the lowering of CSF pressure spinal perfusion may be maintained during critical moments such as placing of the aortic cross-clamp during aortic aneurysm repair. The best safe guard against iatrogenic spinal cord infarction, however, is highly skilled surgical and anaesthetic practice.

Spinal epidural and subdural haematomas should be decompressed acutely by a spinal surgeon or neurosurgeon. Spinal AVMs and cavernomas can be excised. However, the majority are not amenable to this approach. Interventional radiology is the treatment of choice for dural fistulae and intradural AVMs.

The prognosis for functional recovery in established spinal infarction is poor with significant functional recovery leading to ambulation in well under 50% of those affected. The prognosis for spinal haemorrhage is more variable. In the case of compressive epidural and subdural haematomas it is dependent on the rapidity of decompression. In intradural bleeding it depends greatly on the site and source of bleeding. Haematomas caused by high-flow intradural AVMs are often catastrophic. The effects of bleeding from cavernomas may be milder and disability often progresses over many years. The natural history of cavernomas is still poorly understood and therefore the decision when and whether or not to intervene remains problematic.

Hereditary spastic paraplegia

Hereditary spastic paraplegia (HSP) denotes a heterogeneous group of inherited disorders characterised by progressive spasticity and weakness predominantly affecting the lower limbs. The transmission may be X-linked, autosomal dominant or recessive and they may be divided into pure (uncomplicated) and complicated forms. In the former there is only spinal involvement but the latter are associated with other neurological abnormalities.

In pure HSP patients present with steadily progressive gait disturbance or, in childhood, with delayed motor milestones. There is usually progressive spasticity of the lower limbs with hyper-reflexia and extensor plantars. However there may be little or no pyramidal limb weakness and examination tends to be characterized by dissociation between the severity of the spasticity and relatively mild weakness. Rarely, there may be wasting of intrinsic muscles of the feet, urinary disturbance with urgency, frequency and hesitancy, anal sphincter disturbance, sexual dysfunction, pes cavus or mild proprioceptive impairment. Spasticity predominantly affects the lower limbs; there may be mild signs in the upper limbs.

In complicated HSP, spastic paraparesis is associated with other neurological manifestations in a variable phenotype. These may include optic atrophy, retinopathy, extrapyramidal involvement (choreoathetosis, dystonia and rigidity), cerebellar signs (ataxia, dysarthria and nystagmus), cognitive impairment, sensorineural deafness and epilepsy. Peripheral neuropathy, amyotrophy, icthyosis and cardiomyopathy may also be associated (Tables 15.13, 15.14 and 15.15).

Investigation and mangement

Spinal and cranial MR imaging are typically normal but there may be cord atrophy in some forms (e.g. SPG6 and 8). In complicated forms, imaging may show cerebral and cerebellar atrophy or hypoplasia of the corpus callosum.

The age of onset varies from infancy to the eighth decade but is usually between the second and fourth. Prognosis is variable between families and to a lesser extent within families. Early onset HSP (>35 years) tends to be slower in progression and most

Table 15.13 X-linked forms of HSP.

SPG1	Xq28	Mutations in L1CAM, one of a sub-group of integral transmembrane glycoproteins that mediate cell adhesions at cell surfaces	Different mutations give rise to syndromes of MASA (mental retardation, aphasia, shuffling gait and adducted thumbs)
SPG2	Xq22	Mutation in proteolipid protein (PLP) which is a major myelin protein affecting oligodendrocyte function	Gives rise to both pure and complicated forms. Same locus as Perlizaeus-Merzbacher disease. Complicated forms include cerebellar syndromes and mental retardation
SPG16	Xq11.2		Both pure and complicated forms associated with motor aphasia, impaired visual acuity, mild mental retardation, bowel and bladder involvement

Table 15.14 Common autosomal dominant forms of HSP.

SPG4	2p22-p21(multiple SPG4 mutations including point mutations, small insertions and deletions)	Spastin (an AAA protein which acts as a protein chaperone in assembly and function of protein complexes. Involved in motor axonal regulation in corticospinal tracts)	<45% of AD forms of HSP. Usually pure but may be complicated and associated with cognitive impairment, sensory neural deafness, thin corpus callosum, cerebellar atrophy, ataxia, dysarthria
SPG3A	14q11–21	Atlastin involved in axonal development and trafficking	Both early and adult pure and complicated forms may cause a form of cerebral palsy
SPG6	15q11.1	NIPA 1 (may encode a membrane protein)	Adolescent or adult onset form, progressive uncomplicated HSP
SPG10	12q–13	KIF5A (defect in microtubule mediated trafficking leads to axonal degeneration)	Early and adult onset forms
SPG13	2q24–34	Heat shock protein 60 (part of mitochondrial complex, regulates correct protein folding)	Pure HSP
SPG17 (Silver's syndrome)	11q12–q14	Aggregate formation leading to neurodegeneration	HSP associated with wasting of intrinsic hand muscles
SPG31		Receptor expression enhancing protein 1 (REEP1)	Third most common form of AD HSP after Spastin and Atlastin
SPG33		Zinc finger domain containing protein 27 (close interaction with Spastin	
SPG9	10q23.3–q24.2		Complicated forms of HSP including bilateral cataracts, GI reflux, persistent vomiting, distal amyotrophy secondary to axonal motor neuropathy
SPG8	8q23–q24		Pure but fairly severe and occasionally associated with sensory involvement, bladder symptoms and pes cavus

Table 15.15 Common autosomal recessive forms of HSP.

SPG7	16q24.3	Paraplegin (AAA mitochondrial protein – role in activation of respiratory chain complex)	Accounts for <4% of all recessive and sporadic cases. May be pure. Complicated forms associated with dysarthria, dysphagia, optic disc pallor, axonal neuropathy, cerebral and cerebellar atrophy. Muscle biopsy shows features characteristic of mitochondrial disease (ragged red fibres)
SPG5	8q11.1–q21.2		Uncomplicated pure HSP with onset <20 years
SPG11	15q13–15		Most common form. Complicated forms – with cognitive impairment, thin corpus callosum, dysarthria, nystagmus
SPG14	3q27.28		Complicated forms – with cognitive impairment, distal motor neuropathy.
SPG15 (Kjellin's syndrome)	14q22–24		Complicated forms – with pigmentary maculopathy, distal amyotrophy, dysarthria, cognitive impairment
SPG20 (Troyer's syndrome)	13q12.3	Spartin (role in intracellular protein trafficking)	Complicated forms – with dysarthria and intrinsic hand muscle wasting and weakness
SPG23	1q24–q32		Complicated forms – with prematurely aged facial appearance, hypopigmentation, microcephaly, cognitive impairment
SPG24	13q14		
SPG25	6q23.3–q24.1		
SPG26	not known		Complicated forms – with wasting and weakness of intrinsic hand muscles, mild cognitive impairment
SPG27	10q22.1–10q24.1		
SPG28	14q21.3–q22.3		Pure HSP
SPG30	2q37.3		Complicated forms – with neuropathy, cerebellar signs, optic atrophy

patients remain ambulant throughout their lives. However, later onset forms (>35 years) tend to be associated with more rapid disease progression with many patients becoming wheelchair bound in their sixties and seventies. There is no effect on prognosis according to the mode of transmission.

Management is entirely symptom-based, with anti-spasticity drugs, physiotherapy and sometimes botulinum toxin.

Metabolic disease of the spinal cord

Many metabolic disorders can lead to spinal cord disease. The commonest, subacute combined degeneration of the cord (SACD) is discussed briefly here (see Chapter 18 for other causes). SACD, caused by vitamin B_{12} deficiency presents as a myelopathy with prominent dorsal column features. Those typical are distal paraesthesiae and gait unsteadiness, mild upper motor neurone lower limb weakness, depressed knee and ankle jerks, with extensor plantars – and importantly, impaired joint position sense. Retinal haemorrhages and optic atrophy may develop with the macrocytic anaemia, and possibly dementia, as a rare, isolated effect. The typical picture of SACD leads many experienced physicians to give therapy immediately, even before serum levels are known. Treatment is with hydroxocobalamin, a minimum of 1000 μg weekly by injection for the first 3 weeks followed by 1000 μg monthly injections for 6 months, and thereafter 1000 μg every 3 months, for life. Early hydroxocobalamin treatment tends to reverse neuropathic symptoms (and the anaemia) but rarely the myelopathy. There are case reports of severe SACD being helped temporarily by high-dose steroids. Before the various B_{12} therapies, Addisonian pernicious anaemia was usually fatal within 5 years of diagnosis.

Neurological investigation of SACD may reveal dorsal column T2 signal changes on MRI (Figure 15.27). The CSF fluid is typically normal. Haematological and gastro-enterological studies indicate a macrocytic blood picture, usually with anaemia and megaloblastic bone marrow changes, with vitamin B_{12} malabsorption, most commonly caused by Addisonian pernicious anaemia, though there are many potential causes. Nerve conduction studies show an axonal sensorimotor neuropathy. Somatosensory potentials are usually delayed.

The spinal cord pathology of SACD at autopsy reveals degeneration of myelin and axons. Gliosis is not prominent unless the case is very long-standing.

The exact mechanism of cord damage in vitamin B_{12} deficiency remains unclear. Vitamin B_{12} is the cofactor for conversion of homocysteine to methionine and is essential for conversion of methylmalonyl-CoA to succinyl-CoA. Unlike folate, vitamin B_{12} is not known to participate in purine synthesis and thus directly in DNA synthesis. High levels of folate (e.g. folic acid given therapeutically) can circumvent impairment of DNA synthesis caused by vitamin B_{12} deficiency; this can obscure the haematological

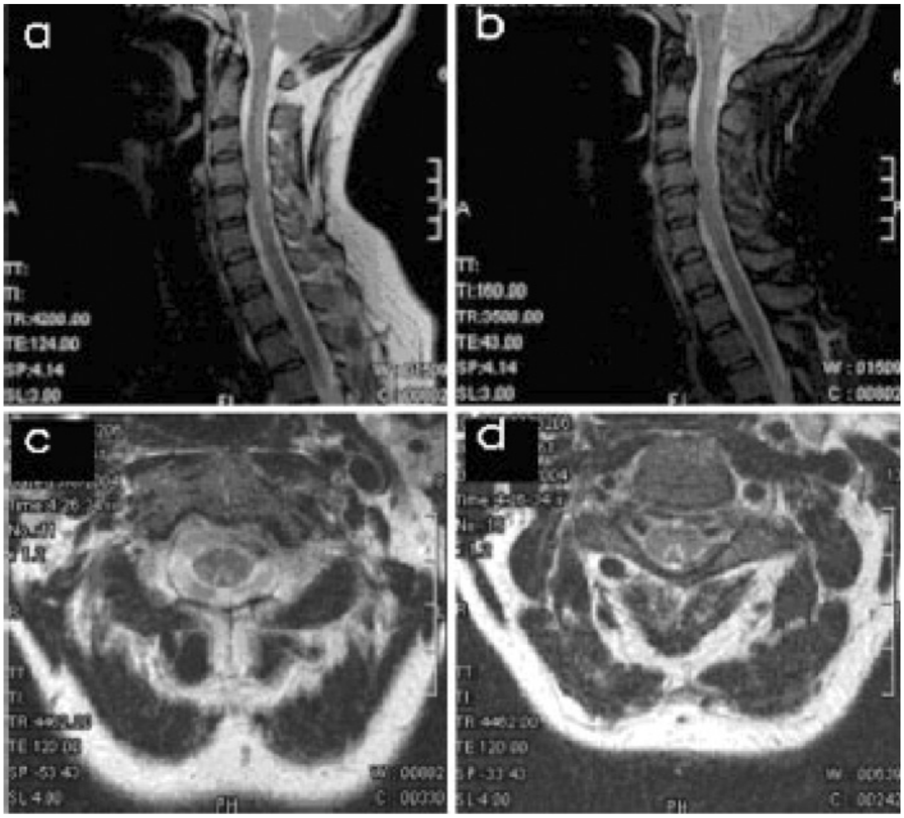


Figure 15.27 Sagittal and axial magnetic resonance images (MRIs) of cervical spine (T2-weighted) showing signal change in posterior columns in a case of subacute combined degeneration of the cord.

picture, which may remain or revert to normal, while neurological signs progress. Neurological features (SACD) can also, if rarely, develop independently of macrocytic anaemia. Thus it seems unlikely that problems with purine synthesis alone are responsible for the neuropathology. It is possible that demyelination results from abnormal incorporation of methymalonate and methylpropionate (precursors of cobalamin-dependent synthesis of succinyl-CoA) into branched-chain fatty acids. Methionine deficiency secondary to failed conversion from homocysteine may lead to impaired synthesis of myelin phospholipids. These mechanisms remain speculative.

Rare metabolic disorders can also cause low serum B_{12} levels, such as congenital transcobalamin II deficiency. Another important consideration is normal serum vitamin B_{12} levels with apparent SACD. Such cases are well described. In some, there is elevation of serum homocysteine and methylmalonic acid. There are also well–recognized situations in which nitrous oxide anaesthesia or recreational drugs appear to provoke features of SACD. Exposure to nitrous oxide irreversibly inactivates cobalamin. Detailed metabolic investigation of the B_{12} pathway is indicated in such cases. Correlation between serum vitamin B_{12} levels and neurological features can be weak: no one should be discouraged by normal serum B_{12} levels from giving hydroxocobalamin to a patient with physical signs suggestive of SACD (hydroxocobalamin is, after all, harmless). Copper deficiency (Chapter 18) can also, if exceptionally cause a similar clinical picture.

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16 Cerebellar Ataxias and Related Conditions

Nicholas Wood

Ataxia derives from the Greek, meaning quite simply, disorder. In neurology the word is used to describe incoordination of muscular activity associated with dysfunction of the cerebellum and its connections. The causes of cerebellar dysfunction are numerous and impossible here to cover in great depth. This chapter thus adopts a structured approach to assessment and management of the ataxic patient, with descriptions of the main disorders affecting the cerebellum. There have been numerous classifications applied to the ataxias; none is without significant drawbacks. The approach used here is clinical, describing how one can sort through the differential diagnosis of an ataxic syndrome in a way that is systematic, robust and efficient.

Approach to the patient with ataxia

Symptoms

The assessment of the patient with possible ataxia begins as they are seen to walk, when one can observe the gait and the ability, or otherwise, to sit down smoothly into the chair. As the symptoms are elucidated there is time to catch the explosive cerebellar dysarthria. However, many patients with ataxia have abnormalities in other neurological pathways in addition to those in the cerebellar system, so one may hear a spastic or dysphonic quality to the speech that can complicate the picture. The specific symptoms of cerebellar disease are problems with balance and general coordination of limbs. Occasionally, this might be best described as a feeling of disequilibrium, even called dizziness by the patient. They may have noticed a speech disturbance themselves or quite frequently this has been pointed out by family or friends. Limb ataxia may first be hinted at by the patient's deteriorating handwriting or that there is difficulty carrying a glass of fluid, or a tremor. Vertigo is generally more suggestive of neoplastic, inflammatory and vascular disease rather than the more slowly progressive degenerative processes.

It is useful to determine the age at onset and the course, including the mode of onset, e.g. a sudden rather than insidious course. An acute history may suggest a cerebellar haemorrhage. A haematoma is often associated with acute raised intracranial pressure symptoms and appropriate signs. If these features develop more slowly in the ataxic patient, then space-occupying lesions including a tumour or even an abscess should be considered and excluded by imaging.

The age of onset helps focus the differential diagnosis. Table 16.1 gives an outline of the sorts of diseases one considers in each category. In the field of ataxia, any symptom occurring in a patient over the age of 25 years is classed as late onset. The pattern of onset and subsequent course also helps sifting the diagnostic possibilities. The length of the history should be established and it is worth asking about early motor milestones and athletic ability at school, which can indicate a much earlier onset than previously appreciated.

Having determined the mode and age of onset, concentrate on quantifying the current problems, how and when they emerged, with a particular emphasis on any extracerebellar features. This should include assessment of cognitive, sensory and any neuromuscular features.

Genetics has a significant role in the aetiology of ataxia: a detailed family history is required, even in the case of apparently sporadic ataxia. The family history details need a broad approach; many of the inherited ataxias are complicated and it is possible that an affected relative may have presented with a clinical picture very different from the proband.

Vomiting, headache or vertigo frequently suggest a posterior fossa mass lesion. Direct questioning should also cover the urinary system, skeletal deformities and cardiac disease. A detailed enquiry of drug ingestion, for both medical and recreational purposes, including alcohol, and occupational exposure is also required.

Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

Table 16.1 Differential diagnosis of ataxia based on age and pattern of onset.

Course	Chronic/insidious onset ataxia	Subacute cerebellar syndrome	Acute cerebellar syndrome
Early	Congenital ARCA	Infective e.g. abscess Raised ICP Post-infectious Some drugs/toxins	Some infections and vascular causes
Adult	Alcohol ILOCA ADCA MSA-C Gluten ataxia FXTAS	Paraneoplasia SOL	Vascular causes

ADCA, autosomal dominant cerebellar ataxia; ARCA, autosomal recessive cerebellar ataxia; FXTAS, Fragile X tremor ataxia syndrome; ICP, intracranial pressure; ILOCA, idiopathic late onset ataxia; MSA-C, multiple system atrophy Type C; SOL, space-occupying lesion.

Physical signs

The examination has two main aims: to establish and delineate the cerebellar features and to determine the presence of involvement of other systems both in the CNS and other organs.

By the end of the clinical history, one has usually formed a good idea of the diagnostic possibilities, with a clear assessment of gait and speech. More formal gait assessment should include any additional features, such as signs of parkinsonism or dystonia, Rombergism and any suggestion of pyramidal or neuropathic signs.

At the bedside the assessment of the extraocular movements is vital. It is extremely rare to see a patient with a cerebellar cause for their symptoms who does not have some abnormalities in the extraocular movements. However, it may be necessary to search hard for such signs. In the primary position the presence of square wave jerks should be assessed. The assessment of ocular pursuit usually reveals a broken jerky quality, because of insertion of saccades into attempted pursuit. At its most extreme, one cannot obtain any normal pursuit; the eyes move entirely by using the saccadic system. One can choose to stress this system more by assessment of the ability to inhibit the vestibular ocular reflex. Nystagmus may be found, and although this is the best known of the cerebellar eye signs is far from present invariably. The saccadic system should also be assessed both by eliciting voluntary saccades – with the instructions ‘look left, look right’ – and reflex saccades where one presents a target. Using these two methods one can assess the speed of initiation, the accuracy and the velocity of the saccades. Typically, in the patient with cerebellar problems there are dysmetric saccades, either hyper- or hypo-, which are demonstrated by undershoot or overshoot, with a small corrective saccade to reach the target. A discrepancy between voluntary and reflex saccades may indicate the emergence of a supranuclear gaze palsy or oculomotor apraxia. Some of these assessments at the bedside can be difficult and a true quantification can only be obtained by electrophysiological assessment, but this is only rarely necessary. In some of the rarer complicated ataxias one can see ophthalmoparesis – this is most common in mitochondrial disease and autosomal dominant cerebellar ataxias (ADCAs). The presence of opsoclonus may suggest paraneoplastic disease in an appropriate clinical setting. Downbeat nystagmus with symptoms of vertical oscillopsia suggests a structural lesion at the foramen magnum.

Ophthalmoscopy is necessary to assess the optic nerve, retina and macula, looking for signs of atrophy or pigmentary changes.

The classic limb signs of cerebellar disease in the upper limbs include intention tremor, dysdiadochokinesis, rebound and finger–nose incoordination, where one may observe dysmetria and past pointing. In the legs an assessment of heel–shin coordination usually suffices. It is quite usual to find that the legs are more severely affected than the arms (see Chapter 3).

Additional signs

Assessment of other systems should include signs of dysmorphism, skeletal abnormalities especially pes cavus and scoliosis, skin rashes and organomegaly. Neurologically, a full analysis of the other systems should include assessment of the pyramidal tracts, sensory impairment, neuropathy, extrapyramidal and autonomic features. The latter can be quickly assessed at the bedside by measuring supine and standing blood pressure (BP). It is best to measure BP at 1-minute intervals, for 3 minutes. If there is further concern a more formal and detailed assessment can be carried out.

Investigations

In certain ataxic disorders specialized ancillary tests are required; these are discussed later in the chapter. Here the broad approaches to investigating the ataxic patient are mentioned.

Imaging

High-quality MRI has revolutionized practice generally. It is clearly useful in determining the presence and often nature of any

Table 16.2 Blood tests and the ataxic patient.

Blood test	Purpose	Notes
Routine blood tests (including thyroid function)	General investigation, and may show evidence of multi-system disease	Hypothyroidism is a very rare but treatable cause of ataxia
Autoantibodies and anticardiolipin	SLE, Sjögren's and antiphospholipid syndromes	Often subacute and complicated phenotype
Antigliadin and endomysial antibodies	Coeliac disease and gluten ataxia	Common in general population, so care not to overinterpret
Vitamins, especially B and E	Thiamine, B_{12} and vitamin E deficiencies:	All associated with ataxia
Antineuronal antibodies	Various cancers associated with subacute and/or aggressive cerebellar syndromes	(see Table 16.6 and Chapter 20)
Leucocyte enzymes	In particular, hexosaminidase A	Often concomitant LMN syndrome
Very long chain fatty acids	A variant of adrenomyeloneuropathy	Gene test is also available
Ammonia and lactic acid	Metabolic ataxias	Consider in early onset often subacute and variable phenotypes
Gene tests	See text for specific details	Becoming increasingly important for sporadic ataxia cases; SCA6 and FRDA should be considered

FRDA, Friedreich's ataxia; LMN, lower motor neurone; SLE, systemic lupus erythematosus.

space-occupying lesion. MRI can readily identify haemorrhage; this is also the investigation of choice if inflammatory causes are being considered. However, once these more common aetiologies are excluded, imaging plays a relatively small part in the assessment of the ataxic patient. In the long differential of the degenerative forms of ataxia, MRI will often show non-specific cerebellar atrophy, with or without brainstem or more generalized atrophy, all too often hard to quantify. Research methods are being developed to address some of these deficiencies, but they are not yet in clinical service.

Electrophysiological tests

While imaging helps to define structural anatomy, a range of electrophysiological tools can be used to clarify the functional integrity of the cerebellar system. In assessing a complicated ataxia of uncertain origin, appropriate neurophysiological tests can be helpful. It is often wise to consider:

- Is there a subclinical neuropathy?
- Does the visual system require interrogation with evoked responses or electroretinography?

Somatosensory evoked responses and central motor conduction times may also prove useful.

The finding of an associated neuropathy is especially useful in the assessment of degenerative causes. For example, early onset ataxia with a significant sensory neuropathy may suggest either Friedreich's ataxia, ataxia telangiectasia on abetalipoproteinaemia. In later onset cases, and some rare genetic forms of ataxia, an inflammatory cause such as Sjögren's disease needs to be excluded.

Blood tests

There is a long list of potential tests that can be considered (Table 16.2), much as one would for complicated neurological disease of other causes, but there are some that deserve special mention here. Despite their rarity, it is always worthwhile considering the treatable, so an assessment of B vitamins and vitamin E should not be forgotten. Hypothyroidism is frequently mentioned as a cause of ataxia; this is extremely rare. A range of antibody tests are now frequently employed, including an autoantibody screen, antiphospholipid syndrome, antineuronal antibodies and assessment for sensitivity to gluten. An assessment of lysosomal and other enzymes may also point to a specific neurometabolic disorder; hexosaminidase A is of particular relevance to the ataxic patient. There are now numerous gene tests widely available; these are discussed in more detail below.

Ancillary tests

If an inflammatory disorder of the nervous system is being considered an assessment of intrathecal oligoclonal immunoglobulins may help (Chapter 10). These are found not only in cases of multiple sclerosis but also in paraneoplastic disorders (Chapter 20) and other rarer inflammatory conditions such as neurosarcoidosis (Chapter 25). Autonomic features, such as postural dizziness and urinary urgency, may require a detailed assessment of the autonomic system, to both aid the diagnosis and guide treatment. Occasionally, electrophysiological assessment of anal sphincter denervation may point towards a diagnosis of multiple system atrophy. In patients with early onset ataxia of a complicated nature, including severe epilepsy, myoclonus and/or cognitive decline it may be necessary to perform biopsies of axillary skin and muscle.

The ataxic disorders

There are several different ways of structuring discussion of the causes of ataxia. Here, whether or not a condition is inherited or acquired is used as the main dividing line, but even this is not always straightforward. As new genes are discovered, some patients previously thought to have sporadic acquired disorders move into the inherited group. Similarly for congenital causes there are intrauterine events or processes that can produce a syndrome reminiscent of another patient with a genetic cause.

Inherited ataxia syndromes

Congenital ataxias

This group of disorders, as the name implies, encompasses ataxic disorders of early onset; generally these are non-progressive. The clear identification of such early life onset in a developing infant is not always easy, and similarly the definition of non-progression in the growing child also presents difficulties. Moreover, as improvements in our understanding of the genetic bases of these disorders has developed it has become clear that the majority of these disorders have a genetic cause.

There are a number of well-recognized syndromes (Table 16.3) with a range of additional features including involvement of other organs and dysmorphism. The clinical clues that one might be dealing with a congenital problem include developmental motor delay; this can sometimes become apparent by a longer time than normal that a toddler spends crawling before taking independent steps. The demonstration of non-progression is difficult; as a child develops they acquire motor skills. To measure non-progression against this moving background is problematic. Frequently, the history is that of a child, who although able to acquire new skills is always behind their peers and described as clumsy. As motor skills are acquired the child may actually report fewer problems with unsteadiness. Imaging can sometime help in some syndromes and there may be significant reduction in cerebellar volume, including signs such as 'molar tooth' an abnormally deep interpeduncular fossa with elongated, thick, and maloriented superior cerebellar peduncles. The combination of a very small cerebellum and associated structures on imaging in a child who is not profoundly ataxic points strongly towards a congenital explanation.

Other possibilities to be considered in these early onset cases are those caused by developmental abnormalities. Most of these are readily diagnosed with modern imaging techniques and include Arnold–Chiari malformation and Dandy–Walker cysts. These are discussed in more detail in Chapter 15.

Autosomal recessive cerebellar ataxias

There is a long list of mutations inherited in an autosomal recessive manner (Table 16.4). Friedreich's ataxia (FRDA) is far and away the most common cause, accounting for approximately 40% of autosomal recessive cerebellar ataxia (ARCA) cases. The remainder are all individually rare and gene tests are still not widely available. As a general rule, onset of the autosomal recessive ataxias is before the age of 20.

Friedreich's ataxia

This has an estimated prevalence of approximately 2/100,000. The condition is characterized by a progressive gait and limb ataxia and a number of additional features including an axonal sensorimotor neuropathy, pyramidal tract involvement, hypertrophic cardiomyopathy, skeletal abnormalities, optic atrophy, deafness and diabetes. Typically, it begins between the ages of 8 and 15 years. There are reported instances of later onset, even as late as the seventh decade; these are the exception. The chief invariable additional feature is the neuropathy, predominantly sensory and progressive.

Following the identification of the gene frataxin by Campuzano and colleagues in 1996, it was shown that the predominant mutation is a trinucleotide repeat (GAA) in intron 1. Expansion of both alleles is found in over 96% of patients. The remaining

Table 16.3 Congenital inherited ataxic disorders. This is an incomplete list; numerous reports of often singular families. There is also some overlap with the autosomal recessive ataxias, some of which have congenital features, e.g. deafness, but have a progressive ataxia. The conditions listed here have, as far as it is possible to determine, non-progressive ataxia.

Syndrome	Additional features	Mode of inheritance	Gene defect
Joubert's syndrome	Episodic hyperpnoea, abnormal eye movements and mental retardation	Autosomal recessive Genetically heterogeneous	*AHI1* gene *NPHP1* gene CEP290 Plus others with established and distinct loci
Gillespie's syndrome	Mental retardation and partial aniridia	Uncertain inheritance	No gene or locus known
Congenital nystagmus	Hypoplasia of the macula in some cases	Autosomal recessive and X-linked	*NYS1–6p* *NYS2*, X-linked and others
Congential hypoplasia and quadripedal gait	Mental retardation and seizures	Autosomal recessive	17p
Paine's syndrome	Spasticity, mental retardation and microcephaly	X-linked recessive ataxia	No gene identified

Table 16.4 Autosomal recessive cerebellar ataxias (ARCAs).

Syndrome	Gene defect	Clinical pointers	Notes
Friedreich's ataxia (FRDA)	GAA repeat (and some point mutations in *FRDA* gene)	Neuropathy, pyramidal signs, skeletal abnormalities, diabetes and cardiomyopathy	Most common ARCA
Ataxia telangiectasia (AT)	*ATM*	Oculomotor apraxia, mixed movement disorder, humoral immune deficiencies, increased cancer risk	Telangiectasia not always present or easily identified
AT-like disorder	*hMRE11*		
Cockayne's syndrome	CS Type A – *ERCC8* gene CSType B – *ERCC6* gene	'Cachectic dwarfism' Mental retardation Pigmentary retinopathy	
Xeroderma pigmentosum (XP)		Increased skin cancer in XP but not Cockayne's	
AOA1	Aprataxin	Oculomotor apraxia	
AOA2	Senataxin	Oculomotor apraxia	Probably second most common ARCA
Hypogonadism	Not known	Hypogonadotrophic hypogonadism	a.k.a. Gordon Holmes' syndrome
Marinesco–Sjögren's syndrome	SIL1 on chr 5q31	Cataracts and mental retardation	
Progressive myoclonic ataxia (Ramsay-Hunt syndrome)	Genetically complex	Epilepsy is frequently associated	Overlaps with differential of progressive myoclonic epilepsy
Behr's and related syndromes, e.g. 3-methylglutaconic aciduria Type III (Costeff's syndrome)	No gene for Behr's yet identified *OPA3* gene	Optic atrophy (OA), spasticity and mental retardation	There are other cases with OA but not Behr's syndrome
Congenital or childhood onset deafness	Genetically complex	Several different families/syndromes reported	May cause overlap with Usher's syndrome
Autosomal recessive late onset ataxia	Heterogeneous	Clinically variable with a range of additional features	Relatively rare

patients have point mutations on one allele in association with an expansion on the other. This has permitted the introduction of a specific and sensitive diagnostic test, as it is a relatively simple matter to measure the repeat size. The normal GAA repeat length varies from 7 to 22 units, whereas the disease range is around 100–2000 repeats; the shorter the length of the repeat the later the onset and generally the milder the disease phenotype.

The frataxin protein has been shown to be involved in iron metabolism within the mitochondria and a number of therapeutic strategies based around improving mitochondrial function are being developed. No treatment to date has been shown to influence disease progression.

Ataxic disorders associated with defective DNA repair

There are several rare disorders characterized at a molecular level by a reduced capacity to repair DNA. The most well known and most studied is ataxia telangiectasia (AT). This produces a mixed movement disorder with the presence of dystonia and chorea in addition to the progressive ataxia. Growth and sexual development can be delayed and mild learning difficulties are common but not invariable. The typical skin and eye lesions (Plate 16.1) usually develop between the ages of 3 and 6 years and are best seen on the conjunctival surface and the ear. AT is associated with abnormalities of both humoral and cell-mediated immunity and is caused by mutations in the *ATM* gene. There are variants of this clinical phenotype with absence of telangiectasia and later onset, also caused by mutations in *ATM*.

A rarer clinically similar disease caused by mutations in *hMRE11* has been identified and is termed AT-like disorder. Clinically related conditions xeroderma pigmentosum and Cockayne's syndrome (Table 16.4) are also caused by defects in DNA repair; they are much rarer and associated with additional features, most frequently skin abnormalities.

Ataxias associated with oculomotor apraxia

There are two genetically distinct but clinically similar disorders associated with the distinctive feature of oculomotor apraxia – ataxia associated with oculomotor apraxia (AOA) Types 1 and 2. AOA is used to describe intermittent failure of the voluntary saccadic system, and should be suspected where the patient uses head thrusts or synkinetic blinking to help initiate a voluntary saccade. AOA1 has been shown to be caused by mutations in the aprataxin gene on chromosome 9p13. This is characterized by the association of ataxia with chorea early in the disease course, oculomotor apraxia, peripheral neuropathy and variable but mild learning difficulties. MRI reveals cerebellar atrophy; serum analysis may show hypercholesterolaemia and hypoalbuminaemia.

AOA2 is very similar clinically and also overlaps with the AT phenotype. Mutations in senataxin have been shown to cause this syndrome. AFP is elevated in virtually all cases and is therefore a useful screen for this disorder. AOA2 appears to be more common than either AT or AOA1, accounting for approximately 8% of autosomal recessive ataxia.

Ataxia caused by vitamin E deficiency

A relationship between spino-cerebellar dysfunction and vitamin E deficiency has been recognized for many years. Many cases have a demonstrable cause for their vitamin E deficiency such as abetalipoproteinaemia, chronic liver disease and malabsorbtive states secondary to cystic fibrosis or bowel resection. Harding and her colleagues in 1985 described a patient with a progressive spino-cerebellar disorder who had isolated vitamin E deficiency with no evidence of malabsorption. The clinical features of this syndrome include progressive gait ataxia, incoordination of the limbs, areflexia and large fibre sensory loss. Homozygosity mapping led to the identification of a gene α-tocopherol transfer protein (αTTP) on chromosome 8q. These patients have an impaired ability to incorporate vitamin E (α-tocopherol) into very low density lipoproteins in the liver. This function is necessary to maintain the adequate circulation of α-tocopherol. A number of mutations have been described, but the mainstay of diagnosis is the measurement of serum vitamin E rather than genetic analysis. Despite its rarity, it is imperative not to miss such a diagnosis because replacement therapy helps to stabilize the situation and in some cases produces improvements. Generally, vitamin E deficiency caused by malabsortion requires substantially higher doses of replacement therapy than those caused by αTTP mutations.

The most severe vitamin E deficiency state occurring in humans is abetalipoproteinemia. The typical presentation is in the second decade, with progressive ataxia, areflexia, posterior column signs; a pigmentary retinopathy may also be seen. It is caused by mutations in the gene encoding a subunit of the microsomal triglyceride transfer protein and is associated with low levels of apoprotein B, which normally carries lipid from the intestinal cell to the plasma. This results in very low levels of circulating lipids, particularly cholesterol, and severe malabsorption of the fat-soluble vitamins A, D, E and K. Serum vitamin E concentrations are either low or undetectable from birth; acanthocytes are usually present in the peripheral blood.

Hypobetalipoproteinemia is a molecularly related but genetically distinct disorder inherited in an autosomal dominant manner and characterized by moderately reduced serum concentrations of cholesterol, triglyceride and low-density lipoproteins. Most patients are asymptomatic but neurologically they may present with ataxia, absent reflexes and proprioceptive deficits.

Other metabolic causes of ataxia

These are nearly all autosomal recessive disorders unless otherwise stated.

Intermittent metabolic ataxias

These may be caused by abnormalities in the urea cycle, amino-acidurias and disorders of pyruvate metabolism. Most commonly, a high ammonia as a marker of urea cycle dysfunction is the explanation. All these conditions have a similar phenotype with ataxia, dysarthria, vomiting, confusion and involuntary movements. Seizures and a variable degree of learning difficulties may also be seen. Precipitants are not always identified but a history of prodromal illness or a large protein load should be sought. Treatment consists of protein restriction and intravenous fluid administration during acute episodes.

Ornithine transcarbamylase (OTC) deficiency is X-linked and is the most common urea cycle enzyme defect. Affected males die in the neonatal period, but severity varies considerably in females, from the presence of severe neurological deficit to no symptoms apart from mild protein intolerance. A heavy protein meal, infection or the prescription of valproic acid therapy can precipitate an encephalopathy in an asymptomatic case.

Amino acidurias including Hartnup's disease also need to be considered in the intermittent ataxias. There is often a super-added involuntary movement disorder, psychiatric disturbance and a variable degree of cognitive decline. A pellagra-like rash may also be seen in this condition. Hartnup's disease is caused by mutations in *SLC6A19* which encodes a neutral amino acid transporter. Some amino-acidurias, including intermittent branched-chain ketoaciduria and isovaleric acidaemia, present in a similar clinical pattern to the hyperammonemias. In contrast to the urea cycle disorders, a high-protein diet and oral nicotinamide therapy may help.

Pyruvate dehydrogenase deficiency (PDH) is rare and genetically heterogeneous, although the majority of cases are caused by mutations in the gene for X-linked E1 α subunit of the enzyme. However, there is a high frequency of manifesting female heterozygotes with a wide spectrum of disease severity because of variable X chromosome inactivation. Generally, it is a disease with an infantile onset although in manifesting females later onset and slightly more benign course can be seen. In addition to the complicated clinical picture of spasticity, seizures and severe learning difficulties, dysplastic features on brain MRI may be seen. The diagnosis is made most readily by assay of PDH activity in cultured fibroblasts.

Very rarely, intermittent ataxia has been reported as a result of multiple biotin-dependent carboxylase deficiencies. The picture is complicated, with generalized seizures, myoclonus, nystagmus and hypotonia. There are associated defects of humoral and cell-mediated immunity. It is important to diagnose by checking serum biotinidase activity as biotin therapy may result in clinical improvement.

Progressive metabolic ataxias

There is a long list of storage and other metabolic disease that can produce ataxia as a component of the presenting features, usually minor. Also, as awareness and diagnostic accuracy is improving most of these patients are identified in early life, in paediatric clinics. The list includes the sphingomyelin lipidoses, metachromatic leucodystrophy, galactosylceramide lipidosis (Krabbe's disease) and the hexosaminidase deficiencies. Also within this group is adrenoleuco-myeloneuropathy, discussed later in this chapter.

A late onset form of hexosaminidase A deficiency may result in a progressive ataxia with predominantly proximal neurogenic weakness. On imaging there is striking and selective atrophy of the cerebellum. Ataxia may also be seen in Niemann–Pick disease Type C, combined with a supranuclear gaze palsy. Sphingomyelinase activity is usually within the normal range, but foamy storage cells are found in the bone marrow. Unlike Niemann–Pick Types A and B, Type C is not caused by abnormalities in the sphingomyelin gene but in the *NPC* gene on chromosome 18. The exact molecular events leading to the mishandling of lipid and cholesterol are unclear.

Cholestanolosis (also called cerebrotendinous xanthomatosis [CTX]) is a rare autosomal recessive disorder caused by defective bile salt metabolism, resulting from a deficiency of mitochondrial sterol 27 hydroxylase encoded by *CYP27A1* gene. It usually begins after puberty and gives rise to ataxia, dementia, spasticity and peripheral neuropathy. Systemically it leads to premature atherosclerosis, cataracts and tendon xanthomas. Treatment with chenodeoxycholic acid and a statin appears to improve serological parameters and stabilization of the disease.

Autosomal dominant cerebellar ataxias

This is clinically and genetically a heterogeneous group of disorders. There are currently some 30 identified loci for the dominant ataxias. These are numbered in the sequence of each locus as it is found. Spinocerebellar ataxia Type 1 (SCA 1) was one of the first neurological diseases to have its gene mapped, reported in 1977. Not all the genes have been identified (Table 16.5a). Some common themes at both a clinical and molecular level emerge. The molecular consequences of the most common type of mutation is an expanded CAG repeat and the salient points are made in Box 16.1.

The dominant ataxias have two broad classification systems, one clinical and the other based on the underlying SCA mutation. Despite the progress in the genetic field, the clinical classification

Table 16.5 (a) The autosomal dominant cerebellar ataxias.

SCA no.	Genetic locus	Gene	Clinical pointers	Notes
1	6p22.3	Ataxin 1 CAG repeat	Complicated, including: neuropathy, cognitive decline, pyramidal and extrapyramidal features	
2	12q24.13	Ataxin 2 CAG repeat	As above, plus slow saccades and neuropathy	
3	14q32.12	Ataxin 3 CAG repeat	As above but a stronger extrapyramidal phenotype	Probably most common worldwide
4	16q24-qter	N/K	Associated with a neuropathy	
5	11q13.2	SPTBN2 beta-III spectrin D		Very rare
6	19p13.13	CACNAIA CAG repeat	Later onset (>45 years) and relatively pure	Point mutations in this gene produce either familial hemiplegic migraine or EA2
7	3p14.1	Ataxin 7 CAG repeat	Complicated, with slow saccades and prominent macular dystrophy	Shows the most marked anticipation in the known SCAs
8	13q21	Kelch-like 1 CTG repeat		Uncertain pathogenicity
9	SCA9	Reserved		
10	22q13.31	Ataxin 10 ATTCT repeat		
11	15q14–q21.3	Tau-tubulin kinase 2 point mutation		Pure ataxia
12	5q32	PPP2R2B CAG repeat	Prominent tremor	
13	19q13.33	KCNC3 point mutations		
14	19q13.42	PRKCG point mutations	Prominent dystonia	
15	3p24.2-pter	ITPR 1		
16	8q23–q24.1	N/K		
17	6q27 TBP	TBP CAG repeat	HD-like features	Rare
18	7q31–q32	N/K		
19	1p21–q21	N/K		May be allelic to SCA 22
20	11	N/K		
21	7p21.3-p15.1	N/K		
22	1p21–q23	N/K		May be allelic to SCA 19
23	20p13-p12.2	N/K		
24	1p36	N/K		
25	2p21-p15	N/K		
26	19p13.3	N/K		
27	13q33.1	FGF14 point mutations		
28	18p11.22–q11.2	N/K		
Unspecified	16q22.1	Puratrophin 1 point mutations		Overlaps SCA 4 region, but not definitively *SCA 4* gene

Box 16.1 Core principles of the polyglutamine tract disorders

- Several neurodegenerative disease are caused by the same type of mutation; namely, an expanded encoded CAG repeat – Huntington's disease, SCAs 1–3, 6, 7, 17, dentato-rubro-pallido-luysian atrophy (DRPLA) and Kennedy's disease
- The CAG repeat is polymorphic in both normal and disease-associated chromosomes. However, once above a critical threshold the repeat becomes more unstable and may expand from one generation to the next
- There is a tight inverse correlation of length of repeat and age of onset
- Anticipation is seen: this is the phenomena of earlier onset and often more severe disease in succeeding generations
- The greatest instability is seen in the paternal line and most cases of anticipation and *de novo* mutation occur on transmission of an allele from father to offspring
- The CAG codon encodes glutamine and this expanded glutamine tract is in some way 'toxic' to adult neurones

The prevalence of the individual disease varies worldwide and is in part determined by the proportion of high normal repeats in the general population. It is believed that this high normal repeat is an occasional feeder of the *de novo* mutations.

Table 16.5 (b) Clinical impact of the autosomal dominant cerebellar ataxias (ADCAs).

ADCA type	Genetic tests (widely available)	Relative contribution to each subclass (%)
ADCA I	SCA 1–3	50
ADCA II	SCA 7	99
ADCA III	SCA 6	50

system proposed by Harding in 1984 remains useful for structuring diagnostic thoughts and the approach to genetic investigation. This clinical classification is divided into three parts, with a roman numeral for each.

ADCA I is characterized by a progressive ataxic syndrome complicated variably, by cognitive impairment, pyramidal signs, supranuclear gaze abnormalities, neuropathy and extrapyramidal signs. It is extremely rare to see all these features in one patient; the burden of involvement within each system varies both within and between families. One needs to bear this in mind when taking a family history. The disease usually starts after the age of 25, although occasional childhood onset has been reported – a feature that is a consequence of anticipation, the result of the unstable and expanding nature of the underlying repeating mutations (Box 16.1).

ADCA II is also complicated; some of the above features may also be seen but it is the macular dystrophy that singles out this disease. This is the rarest of the clinical subtypes; virtually all cases are caused by mutations in the *SCA7* gene.

ADCA III is generally of later onset than the other two subtypes and is a so-called 'pure' ataxia. A note of caution, however: the signs in ADCA I and II emerge with disease progression, so it is sometimes difficult to be sure that a patient and/or their family are truly 'pure' without the benefit of a long history and/or examining other affected relatives. As a rule of thumb, a progressive ataxia without additional features after 10 years duration is strong clinical evidence of ADCA III. The tests most widely used and available are detailed in Table 16.5(b).

Dentato-rubro-pallido-luysian atrophy (DRPLA), an autosomal dominant disorder found mainly in Japan but reported worldwide, has a variable clinical presentation comprising various combinations of ataxia, dystonia, myoclonus, seizures, dementia and parkinsonism. This disorder is another expanded CAG repeat (Box 16.1).

Investigations

The main investigation involves the identification of the underlying mutation. A fairly widely available and relatively simple gene test is now available and should be the first investigation undertaken in suspected cases. However, the clinician should explain to the patient and relative if appropriate the implications of a positive test. This should include the facts that it is inherited in an autosomal dominant fashion, so siblings and offspring are at 50% risk and that the penetrance is high – close to 100%.

Research imaging studies have highlighted some regional differences in patterns of brain atrophy, but none of these are currently useful in the clinical setting. Neurophysiological techniques may be helpful in quantifying the anatomy and a detailed neuro-ophthalmological assessment can be helpful.

Treatment

All these diseases are progressive, currently incurable and with no proven disease-modifying therapies available; however, there is hope. The predominant mutations accounting for at least 50% of cases are caused by an expanded CAG repeat in the coding segment of the gene. This triplet encodes glutamine and these diseases are known as the polyglutamine disorders. As discussed in Chapters 7 and 9, this mutation is also found in other neurological disorders, Huntington's disease and Kennedy's syndrome. This indicates that there is something common in the pathway of neurodegeneration between these clinically distinct disorders; this raises hope that discoveries in one of these diseases will have an impact upon the others.

Genetic forms of episodic ataxia

This heterogeneous group of disorders is characterized by a marked periodicity in attacks of ataxia. There are many of these patients who describe paroxysmal worsening of their disorder. Some will have clearly defined metabolic syndromes, described above. Some have a familial disorder with an autosomal dominant pattern: these are described here. Many more have an ill-defined syndrome without a clear reason for these episodes. The unusual history of such episodes, if their nature is not recognized, often leads to the mistaken view that these are psychological in origin. At a molecular and genetic level, it is perhaps unsurprising that ion channel mutations have been implicated in many of these disorders.

Episodic ataxia Type 1

This is a rare disorder characterized by attacks of brief duration, lasting seconds or a few minutes. The attacks may be frequent; some patients may experience many attacks each day. Attacks may be precipitated by sudden movement or shocks. The condition classically presents in childhood and attack frequency lessens with age, so it is important to seek early life history in older relatives. They are most often associated with peripheral myokymia which can be seen clinically in some, but may require EMG to diagnose.

Mutations in a potassium channel KCNA1 gene have been shown to cause this syndrome. This channel is closely related to the peripheral neuromuscular potassium channel, attacked by autoantibodies in neuromyotonia (Chapters 9 and 20), which also causes myokymia. Treatment success is variable; acetazolamide may help.

Episodic ataxia Type 2

This is more common than EA1; clinically these attacks resemble a form of vertebro-basilar migraine attack. The attacks generally last hours, build up over several minutes and are associated with nausea, vertigo and often vomiting. The patients look pale and unwell. There may be an associated mild headache. The attacks may vary from daily to several months between. Again, attacks become less frequent as the patient enters adulthood. However, unlike EA1 a slowly progressive ataxia usually develops over the years. The typical picture is to see children or adolescents with episodes, with a parent with a more progressive permanent ataxia.

This disorder is caused by point mutations, usually of nonsense type, in the calcium channel gene *CACN1A*. This is the same gene that may cause familial hemiplegic migraine (Chapter 11) and SCA 6 (see above). This phenomenon, where different clinical disorders are caused by different mutations in the same gene, is called allelic heterogeneity.

Treatment by acetazolamide may be useful, but some have had more success with dichlorphenamide. There is no evidence currently that preventing attacks impacts on the progressive component of the illness, but as EA2 is a rare disorder this is hard evidence to obtain.

Other episodic ataxias

There are families reported with episodic ataxia but no evidence of mutations in either of the above genes. EA3 describes a family with vertigo and tinnitus; there is evidence that the disease causing mutation lies on 1q42. EA4 has been used to describe a family with periodic vestibulo-cerebellar ataxia (PATX).

X-linked ataxia syndromes

The ataxic syndromes associated with mutations on the X chromosome are generally rare and usually complicated. Moreover, the clinical picture points to the underlying diagnosis. A variant of adrenoleucodystrophy may produce ataxic features; the presence of a pyramidal leucodystrophic phenotype with a demyelinating neuropathy usually points to the correct diagnosis. A measurement of serum very long chain fatty acids is a useful screening tool and mutations in the underlying gene can be sought. Pelizaeus–Merzbacher disease can produce an early life onset complicated ataxia; mutations or rearrangements of the *PLP* gene can be detected. Neuro-acanthocytosis is described in more detail in Chapter 5; usually ataxia is overshadowed by the involuntary movements of chorea and dystonia. Autosomal dominant, autosomal recessive and X-linked forms have all been described. A wet blood film looking for 'thorny' red cells (acanthocytes) should be requested. The X-linked form, also called McLeod's syndrome, is associated with abnormalities of the Kell antigen.

Mitochondrial ataxia syndromes

The range of disorders that can be caused by mitochondrial DNA (mtDNA) mutations is described in Chapter 9. In brief, mtDNA is entirely maternal in origin so inheritance of any traits caused by mutations in the16.5 kb circular DNA molecule is through the maternal line. Mitochondria are vital for oxidative phosphorylation and any defects in this system can have wide-ranging multisystemic features. Ataxia is quite common in a number of well-characterized mtDNA syndromes. Kearns–Sayre syndrome is an early life (<20 years) disorder of ataxia, progressive external ophthalmoplegia, pigmentary retinopathy and raised CSF protein. Most commonly it is caused by a deletion of approximately 5 kb of the mtDNA molecule. This usually arises spontaneously and is non-transmissible and therefore is generally non-familial. Missense mutations may also cause complicated ataxia phenotypes including neurogenic ataxia and retinitis pigmentosa (NARP), caused by a mutation at 8993 and the point mutations at 3243 (MELAS) and 8344 (MERRF) syndromes. As a general rule, a complicated multi-systemic disturbance particularly those involving dementia, deafness and visual problems with or without lactic acidosis suggests a mitochondrial disease. A muscle biopsy may be required (Chapter 9).

There is also overlap with the so-called Ramsay-Hunt syndrome of ataxia and myoclonus. The differential diagnosis includes MERRF, DRPLA, ceroid lipofuscinosis, sialidosis, and Unverricht–Lundborg disease. Usually, seizures are common in these latter disorders.

Acquired ataxia syndromes

Of the many acquired cerebellar disorders, chronic alcohol abuse is probably the most common, followed by various nutritional deficiencies. The more common acquired disorders are mentioned here.

Infective disease and the cerebellum

In this section, only those infections that give rise to prominent cerebellar dysfunction are discussed. For a more detailed account of CNS infections, see Chapter 8.

Acute or subacute onset

Acute cerebellar ataxia of childhood is the most common illness and although attributed to a viral infection, serological evidence is usually lacking. The usual viral causes include: echoviruses, coxsackie groups A and B, poliovirus, Epstein–Barr and herpes simplex virus. Very occasionally some bacteria produce a similar syndrome.

The condition usually presents between the ages of 1 and 8 years and a mild prodromal illness is sometimes reported. The illness worsens over hours or occasionally days; the child presents with severe ataxia particularly of the midline, with the limbs relatively spared. Additional features include myoclonus, opsoclonus or ocular flutter. Despite this dramatic presentation the outlook is good although it may take several months for full recovery.

Post-infective processes may also affect the cerebellum and its connections. This is particularly well recognized as part of the syndrome of post-infectious disseminated encephalomyelitis after varicella infection. It has also been reported following measles, rubella and mumps. There are a number of brainstem syndromes including Bickerstaff's encephalitis and the Fisher variant of acute inflammatory polyradiculoneuropathy which may present with ataxia, but the clinical picture is complicated by brainstem signs such as ophthalmoplegia.

Progressive ataxia with a chronic or subacute course

Infections causing progressive ataxia are all rare. In childhood, one needs to consider the post-measles complication of subacute sclerosing panencephalitis. This rare but serious condition has a number of other features including myoclonus and cognitive decline. Congenital rubella may produce a pancerebellar syndrome in association with dementia, optic atrophy and occasionally multifocal myoclonus with onset between the ages of 8 and 19 years. HIV infection has become the great mimic and may produce an encephalopathy with ataxic features.

In adulthood there are very few infective agents that produce a progressive cerebellar presentation. Of most importance currently are the various presentations of prion disease. These are discussed in more detail in Chapter 7. Ataxic features are most commonly found in the familial Gerstmann–Sträussler–Scheinker syndrome and in variant Creutzfeldt–Jakob disease. The iatrogenic form of spongiform encephalopathy also produces a predominant ataxic phenotype. This disease resulted from erroneous contamination and inoculation by a variety of means, including growth hormone replacement therapy, corneal and dural grafts. It has become exceedingly rare, following its identification and the important public health measures that ensued.

Cerebellar involvement has also been described following infection by *Mycoplasma pneumoniae*, *Legionella pneumoniae* and *Toxoplasma gondii*, as well as in typhoid fever and tick paralysis. Lyme disease can produce an ataxic picture complicated by bilateral facial palsy and cerebrospinal fluid (CSF) lymphocytic pleocytosis. A number of tropical infections also need consideration in the appropriate clinical setting. A transient cerebellar syndrome lasting several weeks and resembling acute cerebellar ataxia of childhood has been reported following *Plasmodium falciparum* infection. Cerebellar signs, particularly gait ataxia, are common in the racemose form of neuro-cysticercosis (Chapter 8).

'Vanishing white matter disease' is one of the more prevalent inherited childhood leucoencephalopathies and is characterized by progressive neurological decline, and in particular cerebellar ataxia (Chapter 10). However, there is wide phenotypic variability and it may present in adulthood. It is an unusual disease in which there is a genetic defect (in one of five subunits of a translation initiation factor eIF2B) and yet its sensitivity to febrile infections is striking. MRI is usually extremely helpful in establishing the diagnosis

Finally, space-occupying lesions of the posterior fossa associated with fever require urgent imaging to identify the possibility of a cerebellar abscess. These usually present relatively subacutely with headache and symptoms and signs of raised intracranial pressure. TB may produce a more indolent condition.

Inflammatory disease and the cerebellum

An isolated cerebellar syndrome is a rare presentation of multiple sclerosis. MRI shows white matter lesions, which is usually the reason multiple sclerosis is considered. The differential diagnosis of possible demyelinating disease or other inflammatory conditions are discussed in Chapter 10. They include sarcoidosis, systemic lupus erythematosus (SLE) and similar syndromes, antiphospholipid and Sjögren's disease. Investigation needs to be tailored to the clinical impression and but involves appropriate antibody tests, CSF examination, and ancillary tests such as lip biopsy in the case of sicca syndrome.

Vascular disease and the cerebellum

Degenerative cerebrovascular disease can present with an abrupt onset cerebellar and/or brainstem syndrome. The presence of severe headache, raised intracranial pressure and impairment of consciousness suggest the possibility of a posterior fossa haematoma. This is a neurological emergency and requires urgent imaging to determine the necessity for neurosurgical intervention. Outcome is worse if diagnosis is delayed.

Thrombotic and embolic events cause an isolated cerebellar syndrome relatively rarely; commonly there are associated brainstem signs, such as diplopia and vertigo. These conditions are discussed in Chapters 4 and 25.

Vascular anomalies

Cerebellar haemangioblastomas are vascular and cystic tumours that can present as mass lesions with a consequent cerebellar syndrome. The lesion usually takes the form of an expanding cyst, which causes the subacute deterioration. Appropriate imaging and neurosurgical management is usually effective. These tumours rarely bleed spontaneously, but once present do need to be monitored. Generally growth results in progressive symptoms and signs and thus regular imaging is not always required.

These tumours can occur throughout life, but the development of a haemangioblastoma before the age of 40 raises the possibility of von Hippel–Lindau disease (VHL). The presence of two haemagioblastomas or a family history virtually confirms the condition. This is important as the patient and at risk family members will need to be considered for genetic screening. Because VHL is a multisystem disorder this requires neuro-ophthalmological examination for the retinal angiomas, abdominal imaging for multiple organ cysts, renal cell carcinomas and phaeochromocytomas. Twenty-four hour urinary catecholamines are also advised. VHL is inherited in an autosomal dominant manner although there is a significant new mutation rate, so the absence of a family history should not dissuade one from the diagnosis or the need for relative screening once the diagnosis is confirmed.

Other vascular anomalies such as dural fistulae and arteriovenous malformations are discussed in Chapter 4; they are relatively rare causes of an ataxic syndrome.

Chronic bleeding, often from an unknown cause can result in superficial siderosis. This is a rare disorder, more common in males than females (3 : 1) that causes slowly progressive cerebellar ataxia, mainly of gait and sensorineural deafness, often combined with pyramidal signs. It may also be complicated by dementia, bladder disturbance, anosmia, anisocoria and sensory signs. The MRI features are diagnostic, showing a black rim around the posterior fossa structures and spinal cord, on T2 images. These signal changes represent encrustation of the brain surfaces with haemosiderin. Treatment when possible relies on identifying the source of bleeding (see Figure 16.1).

Acquired metabolic disorders

This group includes Wernicke's encephalopathy, hepatic encephalopathy, pontine and extrapontine myelinolysis related to hyponatremia, and hypothyroidism. The latter is only very rarely a cause of a cerebellar syndrome, but as it is potentially treatable it should always be considered. Generally, the other clinical features of these conditions point towards the appropriate investigation and although rare they are all potentially treatable, modifiable or avoidable.

Toxins and physical agents

A large variety of toxins, drugs and other physical agents have been implicated in the pathogenesis of cerebellar disorders. They predominantly cause an insidious onset, slowly progressive clinical syndrome with variable degrees of atrophy on imaging. Direct evidence for causation is not always found and one is often left to take a pragmatic approach to toxin exclusion, where this is possible.

Ethyl alcohol

Ethanol is by far the most common toxin that can produce a cerebellar ataxia (Chapter 18). Acute toxicity produces the well-known effects of staggering gait and slurred speech. Chronic abuse may produce an insidious, slowly progressive gait and limb ataxia with associated dysarthria. From a central pathway point of view, this is generally a pure ataxia without pyramidal signs. However, an alcohol-induced neuropathy is frequently found and this may only be detected with neurophysiology. Imaging usually shows cerebellar atrophy. Lifelong abstinence is strongly advised but even then the disease may continue to progress. However, there is is usually some stabilization and very occasionally mild improvement. Thiamine supplementation is advisable.

Drugs

Antiepileptic medication, especially phenytoin, carbamazepine and the barbiturates, can all cause acute or subacute cerebellar syndrome when the dose is too high. This susceptibility varies from patient to patient and cannot be judged by serum level alone but should be based on symptoms and signs. The latter include nystagmus, dysarthria and gait ataxia. The symptoms may be transient and reflect peak dose levels. There is some evidence that chronic exposure may result in a permanent and progressive cerebellar syndrome in a small minority of cases. This syndrome is usually irreversible although cessation may stop or slow progression.

Lithium toxicity, or as a sequelae to an acute encephalopathy, may produce an irreversible and persistent deficit. There may be a history of an acute precipitant such as starvation or fever.

There is a rare reversible ataxia associated with a variety of drugs, including piperazine (for threadworm), high dose 5-fluorouracil and cytosine arabinoside.

Solvents and solvent abuse

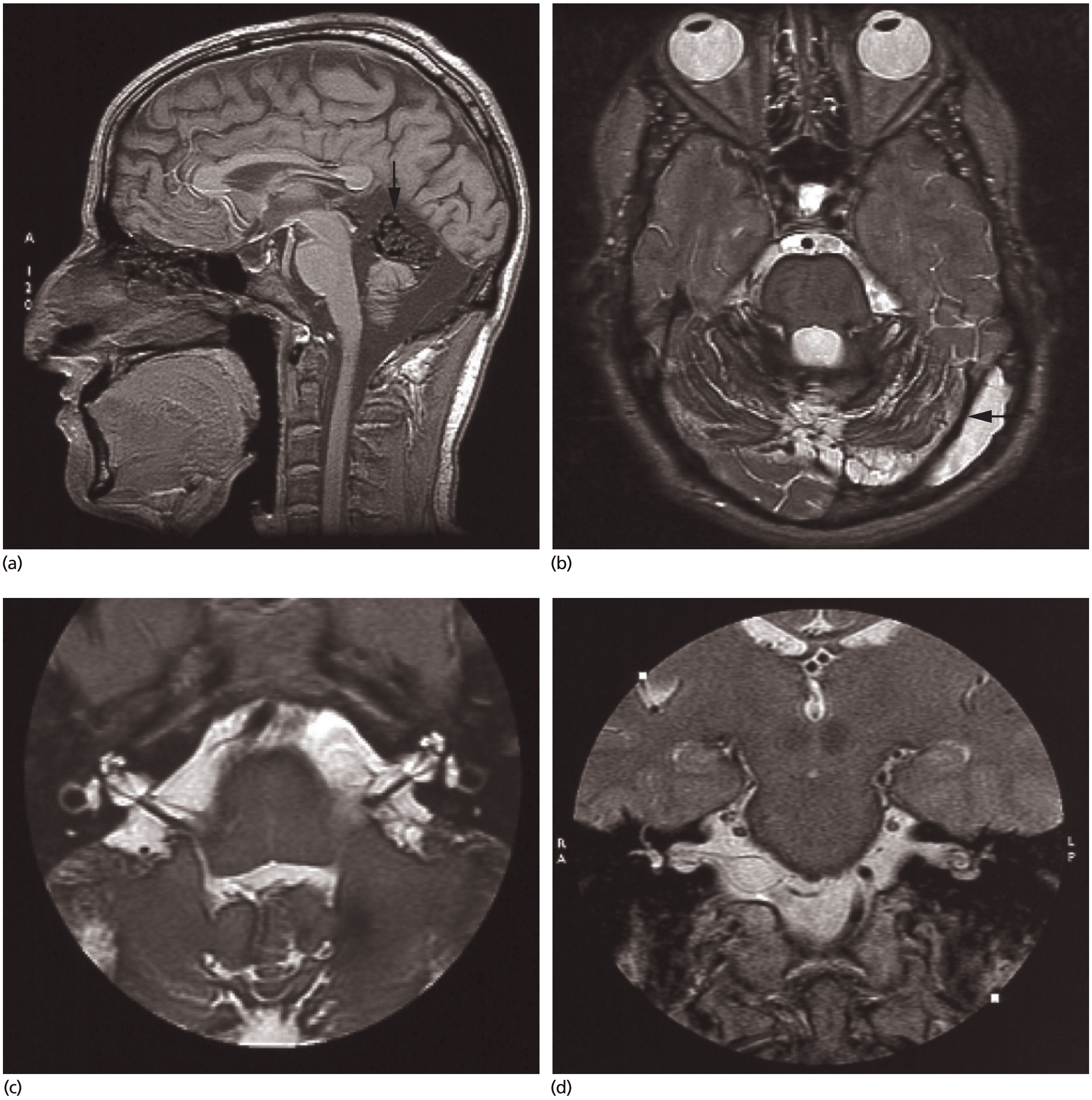
Acute exposure to solvents (Chapter 18) can produce a reversible syndrome but prolonged exposure has been reported to produce a persistent deficit. Additional features such as behavioural problems, confusion, cognitive deficits and even psychosis may be seen.

Heavy metals

In the developed world this is an increasingly rare explanation of the usual progressive and complicated ataxias produced by heavy metals including thallium, lead and methyl mercury (Chapter 18). Features and complications vary. These include distal parasthesiae and cortical blindness (Hg), neuropathic features (Pb and Th) and hair loss (Th). Although often coming on abruptly, features may develop some weeks after exposure.

Physical agents

Hypoxia, heat stroke and hypothermia (Chapter 18) may all produce cerebellar features and at autopsy quite profound Purkinje cell loss may be seen. However, these significant insults often produce generalized cerebral dysfunction which usually dominates the clinical picture.



(a) (b) (c) (d)

Figure 16.1 MR imaging of siderosis in a 38-year-old man with progressive tinnitus, deafness and ataxia (courtesy of Queen Square Imaging Centre). (a) Sagittal MR – hypointensity in cerebellum, with cerebellar atrophy. (b) T2W axial MRI – superficial hypointensity surrounding cerebellum. (c, d) T2W MRI – superficial hypointensity surrounding VIII and V.

Paraneoplastic cerebellar degeneration

This syndrome is quite distinctive (Chapter 20), with generally a subacute onset over weeks and months of midline cerebellar ataxia, usually profound. Typically, patients lose independent mobility within 12–18 months. They may also have chaotic eye movements and oscillopsia. The diagnosis should be suspected in such aggressive cases with onset in later life. Imaging is helpful in that it is typically virtually normal: there are few conditions that produce such unimpressive imaging findings in the face of a major clinical syndrome. Another disease area to consider in this situation is prion-related ataxia.

General health questioning may reveal symptoms such as weight loss, general debility or symptoms suggestive of a primary tumour. There has been substantial progress in our understanding of these disorders and at the time of writing nine specific antibodies have been identified in patients with paraneoplastic cerebellar degeneration (PCD). These are shown in Table 16.6. The major tumours associated with PCD are gynaecological, breast, lung and testicular cancers and Hodgkin's lymphoma. Frequently, the tumours are small and difficult to identify. The role of antibodies (if any) in causation is not clear. It would appear that there is an autoimmune response to the cancer, that may keep the tumour in check, and that this response produces antibodies which cross-react with cerebellar antigens. Management is based on identification and treatment of the underlying malignancy. Immunomodulation, mostly with intravenous immunoglobulin or plasma exchange, has been tried but with variable success.

Late onset cerebellar degenerations

These conditions are probably the largest and least understood group of ataxias that present to the adult neurologist. The aetiology is almost certainly heterogeneous and the syndromes that are recognized vary in some of their features.

Multiple system atrophy

This is the most common clearly defined syndrome, accounting for up to 50% of the late onset cases. MSA usually starts in the sixth to seventh decades and unfortunately is relentlessly progressive, with severe disability within 5–7 years. It may present as a parkinsonian syndrome (Chapter 5), with autonomic dysfunction (Chapter 23) or as a cerebellar syndrome. Whatever the initial presentation other features tend to develop with time, although usually one set of clinical features predominates. Associated extra features include urinary symptoms, postural dizziness and REM sleep disturbance. Additional clinical signs include signs of extrapyramidal disease, these may be mild and need careful clinical assessment to determine, lying and standing BP, antecollis and mini-myoclonus in the fingers.

There is no absolute diagnostic formulation for MSA; the internationally agreed criteria require typical pathological features for a definite diagnosis. MRI may reveal signs of brainstem and cerebellar atrophy and also the 'hot cross bun sign'. This is not entirely specific, but in the right clinical setting does strongly support the diagnosis. Sphincter EMG may also show evidence of denervation, and autonomic function assessment may help both diagnostically and allow appropriate symptom management.

The management of MSA involves a coordination of expertise with input from a multi-disciplinary team. There is no satisfactory drug treatment for the cerebellar features but physiotherapy and other support services can be of benefit.

Ataxia and sensitivity to gluten

This is the relatively newly described syndrome in which patients with mid and later life onset of progressive ataxia have been reported either to have clinical signs or intestinal biopsy features of gluten enteropathy (e.g. coeliac disease), or have a range of antibodies (principally antigliadin) suggesting sensitivity to gluten. This manifests itself as a neurological disease, termed gluten ataxia. However, antigliadin antibodies are non-specific and relatively common in the general population; their actual role in the ataxia remains uncertain. Anecdotally, gluten exclusion does not appear to impact on the progression but large well-designed studies are needed to address this.

Table 16.6 Antineuronal antibodies (after Shams'ili *et al.* 2003).

Antibody	Clinical syndrome	Associated cancer	Immunohistochemistry
Anti-Yo	Cerebellar ataxia	Ovarian, breast	Cytoplasm of Purkinje cells and large brainstem neurones
Anti-Hu	Cerebellar ataxia, PEM/SN	SCLC	Nuclei of all neurones, nucleolar sparing
Anti-Ri	Cerebellar ataxia, OM	Breast, gynaecological, SCLC	Nuclei of all central neurones, with nucleolar sparing
Anti-Tr	Cerebellar ataxia	Hodgkin's lymphoma	Cytoplasm and dendrites of Purkinje cells
Anti-VGCC	Cerebellar ataxia, LEMS	SCLC (60%)	–
Anti-Ma	Cerebellar ataxia, brainstem dysfunction	Numerous	Nuclei and cytoplasm of neurones
Anti-Ta/Ma2	Limbic encephalopathy, cerebellar ataxia	Testicular	Nuclei and cytoplasm of neurones
Anti-CRMP5/CV2	PEM/SN, cerebellar ataxia	SCLC, thymoma, gynaecological	Cytoplasm of oligodendrocytes
Anti-mGluR1	Cerebellar ataxia	Hodgkin's lymphoma	Cytoplasm of Purkinje cells and brush cells, climbing fibres

LEMS, Lambert–Eaton myasthenic syndrome; OM, opsoclonus/myoclonus; PEM, paraneoplastic encephalomyelitis; SCLC, small cell lung cancer; SN, sensory neuronopathy; VGCC, voltage gated calcium channels.

Fragile X tremor ataxia syndrome

This is a very recent addition to the differential diagnosis of mid to late life onset progressive ataxia. Fragile X syndrome is the most common cause of mental retardation in males and is caused by an expanded (non-coding) repeat in the *FMR1* gene. In the 'normal' range of repeats there is a high normal or premutation repeat length (55–200 CGG repeats). Hitherto, this has been considered purely as a substrate for occasional expansion into the disease-associated range and the production of fragile X syndrome in male descendents. Jacquemont *et al.* (2004) reported an excess of pre-mutation carriers in patients with a late onset ataxia syndrome with prominent tremor and associated cognitive decline. Others have confirmed these findings and pathological examination has revealed the presences of novel proteinaceous nuclear inclusions in both neurones and astrocytes. They are ubiquitin positive but dissimilar to the inclusions of Parkinson's disease, Alzheimer's disease and other tauopathies, nor do they resemble the nuclear inclusions seen in CAG repeat disease. Imaging reveals generalized volume loss of cerebrum and cerebellum and signal changes in the middle cerebellar peduncles. Diagnosis of fragile X tremor ataxia syndrome (FXTAS), in appropriately selected clinical cases is by genetic analysis of the *FMR1* repeat.

Idiopathic late onset ataxia

This is an heterogeneous syndrome encompassing the significant proportion of cases of presumed degenerative ataxia in which no cause is found. Typically, the symptoms start in the sixth decade and beyond; patients present with a slowly progressive relatively pure ataxia. There are exceptions, and in particular mild pyramidal signs can be found, but the cerebellar features predominate. The prognosis in this group is generally somewhat better than those with the cerebellar presentation of multiple system atrophy.

Conclusions

The differential diagnosis of the ataxias is long, and often complex. However, there are some basic rules that are a valuable guide: the age of onset, pattern of onset and course provide a quick and fairly reliable initial screen. After these specific questions, the family history, alcohol exposure and additional neurological symptoms often lead to a clear diagnostic shortlist, even before examination. Examination is focused on delineating the cerebellar features and seeking evidence of involvement in other systems. Investigation is then tailored to the emergent differential list.

Unfortunately, the drug treatment of ataxia for either symptoms or disease modification is still very poor. However, there are a small number of treatable or modifiable diseases; these should be rigorously excluded whenever they are suspected. Established balance problems are very resistant to any pharmacological intervention. Supportive therapies such as speech therapy and physical interventions are frequently required. It is hoped that as we further our understanding of the molecular and cellular processes involved that more targeted and rational therapies will emerge.

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17 Restorative and Rehabilitation Neurology

Richard Greenwood, Jon Marsden, Diane Playford, Valerie Stevenson, Nick Ward

While there are many opportunities for the prevention or reversal of disease, health care systems worldwide are dominated by people with chronic diseases and conditions. In the USA for example, patients with chronic conditions account for nearly 80% of health care costs. In the UK, neurological damage accounts for 40% of people severely disabled and who require daily help, and for most of those with complex disabilities resulting from a combination of physical, cognitive and behavioural problems. Any health care system is thus confronted on a daily basis with a demand to meet this need from finite resources.

In these circumstances, when reversal of pathology is incomplete, profound life changes may result. The majority of people can then benefit from delivery of the multi-dimensional process termed rehabilitation by skilled rehabilitation teams; they can then make major physical, emotional, social and environmental adjustments, become more independent and enjoy a better quality of life, and avoid deterioration and secondary complications. Rehabilitation aims to facilitate functional restoration and adaptation, following loss of physiological, psychological function or anatomical structure, collectively known as impairments. It also aims to enhance an individual's functional activity and societal participation, and reduce the impact of limitations in these areas, so that life quality is subjectively improved and life is 'worth living'. Rehabilitation incorporates a post-diagnostic goal-focused learning and problem-solving process using all available means, including therapy approaches, treatment modalities and medical and non-medical treatments, to minimize and prevent the consequences of a disease and facilitate adaptation to change. Although not immediately apparent in the literature, this process is integral to the management of many chronic disorders.

Key aspects of the rehabilitation process include reiterative multi-disciplinary assessment, problem definition and measurement, goal-setting and treatment planning, treatment delivery, evaluation of effectiveness and reassessment with a view to further treatment. Medical and surgical treatments are combined with interventions involving training and skill learning to achieve attitudinal as well as behavioural change, to reduce impairment and functional dependence, and to facilitate social roles and improve quality of life. Skill retraining is largely delivered via physical, occupational, cognitive and speech and language therapies and may include facilitation of adaptation to loss by both the patient and family, the prescription of appliances and environmental modifications, and the development and application of new technologies and service delivery systems. In the context of disorders that affect brain function, particularly well-defined and structured learning techniques are required to achieve skill learning.

In the context of neurological disease, rehabilitation goals are achieved via the prevention of secondary complications; functional compensation, which involves behavioural adaptation and substitution as well as modification of personal, environmental and social contextual factors; and neural restoration and substitution (Table 17.1). These processes often need to be accompanied by the difficult process of adjustment to loss and change, a need that is easily forgotten during the injection of botulinum toxin, a session in the gym or during a functional imaging study.

Rehabilitation is a thus a complex intervention and is delivered via a menu of multi-disciplinary in-patient and community-based service delivery systems which differ by plant, personnel and process. A classification of these different service options, as a rehabilitation typology, remains to be agreed nationally let alone cross-culturally but would facilitate the development of service delivery systems or networks as well as comparisons between different studies. The use of each component of such a network is driven by a number of factors including patient need, resulting from co-morbidities, time since injury, level of dependency, characteristics of the residual impairments and age of the patient, social back-up and resources available. The benefits so far reported of organized complex polymodal in-patient, residential or community-based interventions are likely to reflect the combined effects of preventing the systemic and neurological

Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

Table 17.1 Mechanisms of recovery after neurological damage.

- Prevention of neural and systemic complications and
- Functional compensation via
  - Behavioural adaptation and substitution and
  - Modification of personal, environmental and social contextual factors allow
- Neural restoration and substitution via
  - Resolution of oedema, mass effects and toxic–metabolic dysfunction
  - Diaschisis (i.e. functional changes in brain areas remote from an area of damage)
  - Neural replacement, regrowth and
  - Reorganization of use-dependent neuronal networks

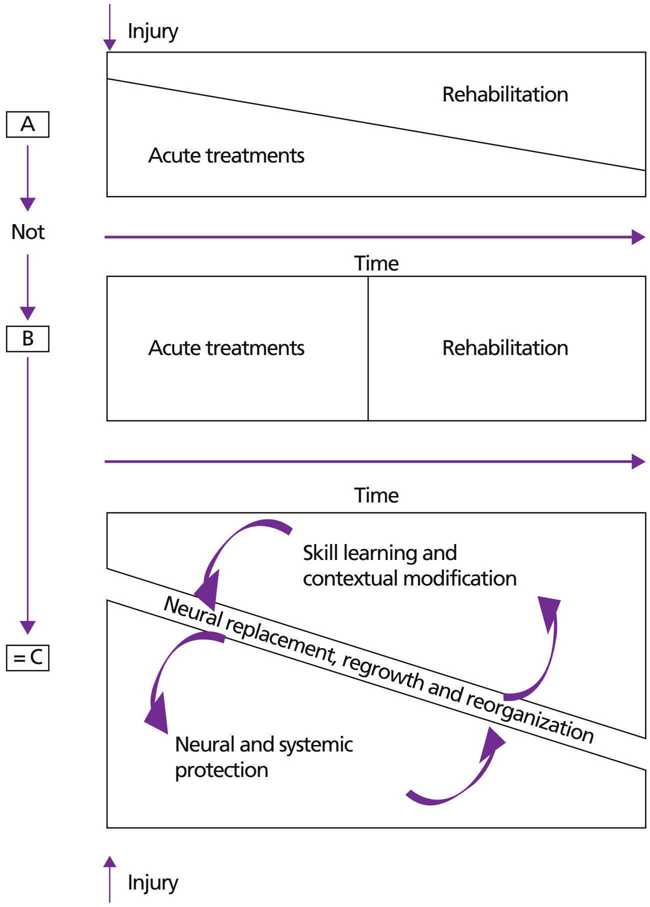

Figure 17.1 Acute treatments focus on neural and systemic protection while rehabilitative strategies, involving skill learning and contextual modification, are derived from practice in post-acute rehabilitation. Optimal outcomes (C) are most likely to result from their use in parallel (A) rather than in series (B), so that complications are prevented and the neurobiological processes contributing to neural restoration can be entrained.

complications described below, and the functional interventions that focus on teaching new skills and the use of aids, appliances and environmental modifications to help patients adapt to their impairments. These facilitate the functional effects of neural restoration and reorganization (Figure 17.1).

The way in which the in-patient and community-based components of rehabilitation service systems are configured, used and linked are driven largely by three different natural histories that result from neurological disease and injury: first, single incident brain and spinal cord damage and acute peripheral paralyses; secondly, deteriorating conditions including late stage multiple sclerosis, Alzheimer's, motor neurone and Parkinson's disease; and, thirdly, static conditions such as cerebral palsy, post-polio syndrome and late effects of other single incident events sometimes acquired in childhood. In-patient and community-based components in each of these three clinical pathways should provide both regional (high-cost, low-volume) and local service options for patients with more or less severe and complex disablement. Coordinated provision of services across health and social care boundaries is essential because most of the work associated with managing any long-term condition is done in the individual's home and community, with only a small fraction occurring in a hospital/residential environment. Both the affected individual and their family, if involved, require encouragement, support and advice to maintain a balanced access to different management strategies. This may fail at certain points during the disease trajectory and require specialist input.

The key to effective longitudinal management is to ensure that interventions are appropriate and timely. This depends on effective and interactive verbal and written communication across health and social care sectors and ongoing involvement with the individual and family. Benchmarks for effective rehabilitation services and a model to guide best practice for the provision of in-patient and community-based rehabilitation, work (re)entry, personal care and support, equipment and accommodation, palliative care and support for family and carers in the context of long-term neurological conditions are summarized in the UK by the Department of Health's National Service Framework (NSF) for long-term (neurological) conditions. This sets out 11 evidence-based quality requirements: 'to improve health and social care services for people with long-term neurological conditions and their carers'. The quality requirements aim to promote quality of life and independence by ensuring patients receive coordinated care and support planned around their needs and choices.

The composition of the multidisciplinary teams that deliver these complex interventions differs depending on clinical need. Cohesive engagement of such a team requires a framework that makes explicit 'who does what, when, where and how' to achieve a commonly agreed aim, via a series of long and short-term goals. Linguistic harmonization between disciplines, particularly between nursing and the therapies in an in-patient setting and health and social services in the community, is crucial to success. In a clinical setting, this framework is provided by both generic and individualizable documentation that reflects a classification, and thus measures, of the consequences of disease. Integrated Care Pathways provide a multi-disciplinary team with generic evidence-based checklists, either process or disease focused,

Table 17.2 Evidence from the basic sciences over the last century initially denied and subsequently confirmed the suggestion that neural repair and reorganization occurred in the CNS after damage. This repair process is facilitated by the prevention of complications and driven by goal-focused task-related training during rehabilitation.

- Donaldson (1895): 'In the central nervous system . . . the cell elements are . . . plastic in the sense that their connections are not rigidly fixed, and they remember. . . . By virtue of these powers, the cells can adjust themselves to new surroundings'
- Cajal (1928): 'In adult centres, the nerve paths are something fixed, ended, immutable; everything may die, nothing may be regenerated. It is for the science of the future to change, if possible, this harsh decree'
- Raisman G. Neuronal plasticity in the septal nuclei of the adult brain. *Brain Res* 1969; **14**: 25–48.
- Finger and Stein (1982): 'Until very recently, prevailing concepts of brain function *precluded* the possibility of structural and neurochemical reorganization of function; theoretically, once damage occurred, the possibility for rehabilitation was to train the patient to use alternative, but less effective, behavioral strategies'
- Neural reorganization in lesioned animals (e.g. Jenkins & Merzenich 1987; Nudo *et al.* 1996) confirmed longitudinally by brain mapping techniques in humans after stroke (e.g. Hamdy *et al.* 1996; Ward *et al.* 2004)

describing core clinical activities underpinning a patient's management longitudinally. They are intended to improve quality of care and reduce clinical risk and variation in standards by prompting and educating health care staff, and to minimize resource utilization. A generic checklist of this type which records the idiosyncrasies of an individual's care as variances should be complemented by a regularly reiterated individualized formulation of a plan of care in which the patient and each member of the team contributes in discussion to an interdisciplinary care plan. This care plan defines and documents at regular intervals the patient's problems, their needs and the action plans necessary to achieve agreed short and long-term goals en route to an overall aim.

These two clinical decision support systems – the care pathway and the care plan – can be computer-based and automatically used as part of the clinicians' workflow. This includes variances which can be fed back to provide actionable recommendations, rather than simply assessments shared with patients at the time and place of decision-making. These are all features that have been shown to significantly improve clinical practice in a variety of contexts, at the level of prescribing practices and serious medication errors, the delivery of preventive care and adherence to recommended care standards.

The effectiveness, compared with historical controls, of organized residential multi-disciplinary care and rehabilitation, was initially demonstrated following spinal injuries sustained in the Second World War. Since then the opportunity to trial the effectiveness of the rehabilitation process has been provided by the high incidence and prevalence of stroke. Trials of different models of care and rehabilitation have shown convincingly that organized care produces better outcomes than disorganized care, a result that has far-reaching implications for health care systems in general. Rigorous evidence to support complex interventions in the context of other acute neurological conditions or as a result of deteriorating or static neurological disorders is sparse by comparison.

The top-down systems approach, often using prospective randomized and blinded group methodologies, has been complemented by bottom-up and largely proof-of-principle investigation of neural reorganization after neurological damage. After initially demonstrating the ubiquity of use-dependent plasticity in controls, these studies have shown that the same process underpins later neurological recovery in the context of disease and are beginning to explore how drivers of neural reorganization can contribute to improved outcomes.

Interest in investigating the process of rehabilitation has arisen from two directions. One has resulted from the need to limit resource use while maintaining or improving quality of care by using project and systems management techniques originally derived from industry. These have been enhanced by cognitive and behavioural explanations about implementation, and the generation of behavioural change to optimize organizational and individual behaviours to achieve best practice. By contrast, advances in the basic and clinical neurosciences (Table 17.2) have provided explanations about how traditional rehabilitative treatments might work. They have been instrumental in changing perceptions of clinicians from a view of therapies from physiotherapy to psychotherapy offered little more than homeopathy to an acceptance of the need to explore and develop rehabilitation interventions at the level of impairment. This chapter explores the delivery and effectiveness of these components of the rehabilitation process in the context of neurological disease.

Neural restoration

The mechanisms underlying a specific limitation in function are complex and result from multiple impairments that may arise from a single lesion in the (central) nervous system. For example, mobility may be affected by leg weakness because of a lack of descending neural drive, spasticity, sensory loss, secondary muscle atrophy, biomechanical changes and compensatory strategies which may develop over time after the initial lesion. Treatment strategies to help patients adapt to their functional limitations have been used for many years, whereas those aimed at minimizing impairments have received less attention. In order to begin to develop current and new treatments for impairment it is imperative to ask whether and how coexisting impairments contribute to a given functional limitation, a task to which the clinical neurosciences can make a unique contribution.

After neural damage, successful restorative therapies are thus likely to require multiple approaches. Neural protection should be aimed both at enhancing neuronal survival and minimizing secondary neural damage, and at facilitating three restorative treatment strategies:

1 Neural replacement;
2 Neural regrowth and regeneration; and
3 Reorganization of functionally useful activity-dependent neuronal networks.

For example, severed axons in the adult mammalian spinal cord can regenerate when provided with an environment that promotes growth using various approaches which include:

1 Cell replacement therapies;
2 Neurotrophic factors to facilitate axonal sprouting and neuronal survival; and
3 Immunomodulation to neutralize inhibitors of axonal growth.

Similar approaches are under consideration in the treatment of brain damage, whether progressive as in Parkinson's disease or multiple sclerosis or single incident following stroke or head injury. The successful application of techniques designed to promote neural replacement and/or repair is likely to require an understanding of the drivers of use-dependent cellular and network remodelling needed to incorporate new tissue into functionally useful networks.

What encourages clinicians and scientists to believe that neural reorganization is an important tool in the restorative therapies? There is now a wealth of evidence suggesting that CNS reorganization at least accompanies and often underpins much of the improvement in impairment that is frequently seen. Experiments in both animals and humans show that many regions in the normal adult nervous system, particularly the cortex, have the capacity to change structure and consequently function in response to environmental change, a process often referred to as plasticity – a basis for skill learning now grounded in evidence. Work using focal brain damage in animal models has clearly demonstrated that for some months after injury, peri-lesional and distant brain regions have an increased capacity for plastic change. Developmental proteins not normally expressed in the adult brain re-emerge in the hours and days following focal brain injury. These proteins are involved in neuronal growth, apoptosis, angiogenesis and cellular differentiation. Structural changes including increased dendritic branching and synaptogenesis have been documented. There is also evidence of peri-lesional and distant cortical hyperexcitability following focal cortical damage, resulting from down-regulation of the α1-GABA receptor subunit and a decrease in GABAergic inhibition. Taken together, these changes suggest that the damaged brain is more amenable to activity-driven changes in structure and consequently function. In other words, the potential for plastic change is greater than in the normal adult brain.

In the human brain, similar injury-induced changes appear to occur. Research in humans is performed largely at the systems level, rather than the molecular or cellular level, using techniques such as functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS). For example, one of the most common and most devastating consequences of stroke is the loss of both power and dexterity in the limbs contralateral to the injury. This occurs when there is damage to the cortico-spinal pathway from the cortical motor system to the spinal cord motor neurones. The majority of corticospinal fibres originate in the primary motor cortex (M1) but there are smaller contributions from other cortical regions. In primates it is known that M1, dorsolateral premotor area (PMd) and supplementary motor area (SMA) are each part of parallel independent motor networks with:

1 Separate projections to spinal cord motor neurones; and
2 Connections to one another at the level of the cortex.

This observation has led to the suggestion that a number of motor networks acting in parallel could generate an output to the spinal cord necessary for movement. It is possible that damage in one of these networks could be compensated for by activity in another. Functional imaging experiments have demonstrated that stroke patients rely on secondary motor regions in the brain such as PMd and SMA to a greater degree when there is damage to the main motor output pathway from M1 to spinal cord motor neurones. However, the projections from these brain regions to spinal cord motor neurones are less numerous and less efficient than those from M1 and thus, although these patients improve as a result of recruitment of these secondary motor regions, they are unlikely to achieve premorbid levels of performance.

The extent of recovery of motor function is at least partially dependent on how much of the normal network is left intact. In the brain of a patient after stroke there is a new configuration of motor networks, less effective than that in the intact brain but which will attempt nevertheless to generate some form of motor signal to spinal cord motor neurones in the most efficient way possible. Longitudinal fMRI studies of stroke patients indicate an initial overactivation in the early stages of many primary and non-primary motor regions during the performance of a motor task. Thereafter, functional recovery is associated with a focusing of task-related brain activation patterns in the same way as is seen during motor skill learning in healthy subjects. The brain activation patterns do not return to normal in all cases but, at least in the motor system, the focusing of activation will tend towards the most efficient system available. One of the roles of restorative treatments is to help this focusing process.

The functional organization of the motor system post-injury will depend most obviously on the extent of the anatomical damage, but within these anatomical constraints there is room for more or less efficient reconfiguration of these networks. Alterations in this efficiency by reorganization, rather than regeneration of tissue, are most likely to underlie therapy-driven reductions in impairment. There are a number of other factors that contribute to this process, which include: how much and what type of

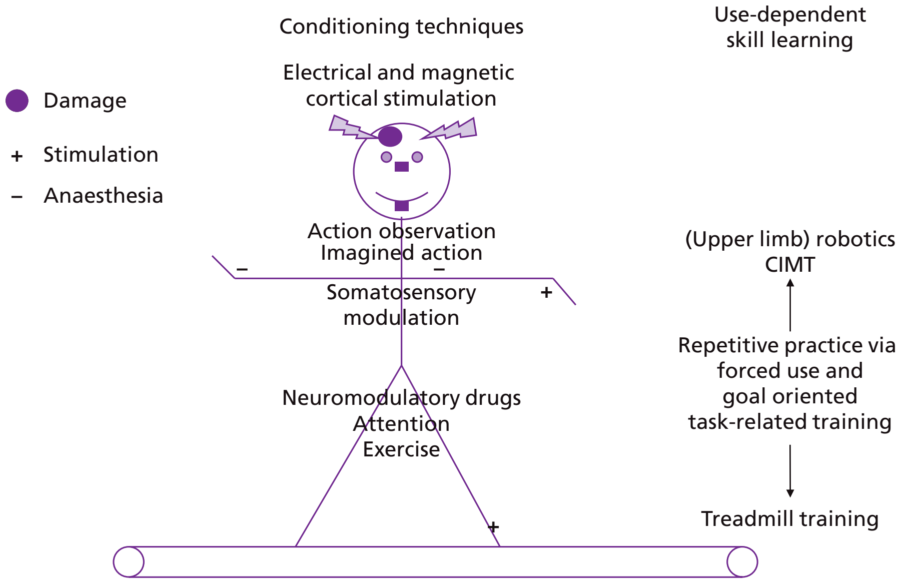

Figure 17.2 Use-dependent and conditioning drivers of neural reorganization that have the potential to enhance functional recovery after neural injury. CIMT, Constraint Induced Movement Therapy.

treatment is delivered, the biological age of the subject, the premorbid state of their brain, current drug treatments and probably their genetic status. All of these factors will influence the potential for activity-driven change within intact brain networks – the proposed mechanism by which functionally relevant brain reorganization occurs.

How does this help us to understand how best to treat the impairment experienced by patients after neural injury? On one level, treatments can be considered as inputs that interact with a system, in this case the damaged brain. The aim of this input is generally to optimize the functional reorganization of the damaged system. An input will succeed in driving functionally useful change only to the extent that the brain regions and networks with which it interacts are intact and are able to influence output pathways. Other treatments are designed to condition the brain to make it more likely that activity-driven change will occur in response to afferent input. For example, repetitive TMS or drugs such as amphetamine will not induce activity-driven change themselves but may enhance the effect of physiotherapy if delivered shortly before a treatment session. Their success will depend on a number of factors relating to whether the networks with which the treatment interacts are intact. For example, repetitive TMS to the affected hemisphere territory M1 is unlikely to have any success in patients with large middle cerebral artery territory infarcts. As yet, the mechanisms of action of these interventions are not well understood but the crucial importance of residual functional anatomy is that it provides a model with which to explore whether and how interventions of different types (Figure 17.2) work in all types of patients.

In summary, successful restorative therapies for patients with impairments secondary to either brain or spinal cord damage are likely to consist of multiple approaches which will include four key elements: minimizing secondary damage, enhancing neuronal survival, facilitating axonal regeneration and behavioural training to organize activity into functionally useful neuronal networks. The aim is for these therapeutic approaches to be targeted towards specific impairments, either singly or in combination, thereby resulting in faster and more extensive recovery.

Therapeutic and task-related training

Non-invasive therapy interventions in the context of neural damage aim to optimize a person's functional ability and may be broadly divided into those that are restorative and those that are compensatory. Restorative approaches aim to improve function via measurable improvement in an underlying impairment, e.g. muscle weakness or dysphasia, and can be contrasted with strategies that aim to improve function by compensating for an underlying impairment which may not change despite measurable improvements in functional activities and social participation. Both strategies may be associated with recordable adaptive changes within neural systems. Compensatory strategies may be external by means of, for example, an ankle-foot orthosis for a foot drop, a communication aid for dysarthria or the modification of a conversational partner's communication style for dysphasia. Alternatively, they may be internal, for example by hip circumduction during walking or alternative dressing strategies to achieve independence in personal activities of daily living (ADL). Compensation for the underlying deficit is not always detrimental and may in fact be the most efficient means of moving or communicating and particularly important in people with long-term progressive conditions.

Early trials comparing the blanket prescription of two physiotherapy approaches or speech and language therapies failed to find clear evidence of effectiveness. This resulted over the last 10 years in an increase in the investigation of the efficacy of individual components and principles underlying type, structure, timing and intensity of training interventions. Functional imaging studies in both animals and humans have shown that adaptive changes within the CNS result from repetition, task-orientation, attention and reward and are specific to the practice and learning of a behaviourally relevant and motivating sensorimotor or cognitive skill rather than simpler repetitive activities. On this basis rehabilitation should focus on the functional activities relevant to each patient's needs, rather than the practice of abstract movement patterns or cognitions.

The applicability of task-related training as opposed to specific impairment-based interventions may depend on the underlying ability and the type of skill being learnt. Progressive resistance training has been compared with a reaching task in groups of patients matched for motor function following stroke. In patients with poor motor recovery, only task-related training resulted in any improvement in upper limb coordination in the paretic limb. By contrast, in patients with better recovery whose kinematics were fairly normal, only progressive resistance training resulted in a decrease in the compensatory trunk movements that often accompany reaching with the paretic limb. However, for other complex skills such as walking, practice of the whole task rather than its component parts may produce the most benefit even in people capable of walking independently following stroke.

Studies on healthy subjects suggest that skill learning may also be optimized by varying practice structure and thus the instructions and support given by the therapist. These factors in turn depend on the environment in which a skill is carried out, the type of skill to be learnt, the stage of learning and the degree to which one wants the skill to be generalized to other situations. Often skills are performed in an unpredictable environment, so-called open skills. Many factors can vary even during the performance of a simple task such as speaking a sentence or picking up a cup: the location of the cup, its orientation, weight and frictional qualities as well the presence of adjacent objects, the availability of sensory cues and the subsequent action such as drinking or placing the cup in a cupboard may all vary. All these factors will affect the planning and execution of the task, requiring for example differences in coordination between reaching and grasping phases, and differences in grip and load forces while manipulating the object. Acquisition of these open skills requires variable practice in which task parameters are randomly changed to reflect the normal variation in the environment. By contrast, skills performed in a predictable environment, closed skills, benefit from constant practice conditions. The type of skill to be achieved can also determine practice structure. The interdependence of successive stages of a skill determine whether breaking a skill into simpler constituent parts that are then practiced individually, termed part practice, will result in an overall improvement in the parent task. This may be effective for certain serial skills that are composed of a string of discrete stages, while it may not be as effective for continuous skills such as walking where each stage is interdependent.

During the initial stages of learning, feedback involving verbal instruction, manual guidance and demonstration of skill may be required as the learner determines what to do, what the goals are, and how to achieve saturation of in-session gains and thus encourage between-session consolidation. However, the use of continuous therapist-derived or augmented feedback about task performance in the later stages of learning may result in the learner becoming reliant on this type of feedback to the detriment of using their own internal feedback via visual, vestibular and somato-sensory information. This can be avoided by techniques such as fading the amount of therapist-derived feedback across trials, or providing feedback only if the task falls outside pre-set criteria. In addition, the type of therapist-derived feedback required for optimal learning in the context of deficits in motor programming or sensory feedback may be determined by lesion location, so that explicit instruction may disrupt implicit motor learning after sensorimotor cortex or basal ganglia stroke but not in healthy controls or after cerebellar stroke.

Evidence for the optimal timing of therapy interventions in humans is scant. Constraint-induced therapy for the upper limb within 14 days of stroke in humans appears to improve arm function, but the initiation of early exercise following a cortical lesion in rats has been reported to result in an increase in the area of damage. By contrast, after incomplete spinal cord injury in rats, a delay of 3 months in the onset of therapy impairs recovery. The point at which therapy should be terminated is equally unclear. After stroke it is often recommended that therapy should finish when patients reach a plateau and fail to respond to rehabilitation. However, this may be partly the result of adaptation to a therapy programme and, as in healthy subjects performing an exercise regime over time, further improvements may be observed after a modification in intensity and/or specific intervention. In this way the potential for reorganization and recovery of function may exist for several or more years post-lesion.

Clear-cut guidelines for the intensity of intervention are also unavailable. A meta-analysis found that augmenting therapy with extra therapy in addition to a normal level of intervention can result in a significant improvement in ADL and walking speed after stroke. The augmented therapy groups tended to receive twice as much input as the control groups, on average an extra 16 hours. Larger effects were seen with increased therapy time and no ceiling effects were reported. Beneficial effects of high-intensity interventions have been reported for constraint-induced therapy where therapy is given for 6 hours a day for 2 weeks but improvements in upper limb function may also be seen with as little as 30 minutes of task-related training a day over a 2-week period. Similar observations have been made in the context of aphasia therapy, usually after stroke. An early meta-analysis and review of trials of speech and language therapies concluded that there was evidence of effectiveness, but restriction of the evidence to randomized controlled trials, compared with no therapy, informal support or another speech and language therapy, failed to find clear evidence of effectiveness. However, increased intensity of therapy is associated with improvement, for example in four studies that provided an average of 9 hours of therapy a week for 11 weeks compared with four negative studies that provided approximately 2 hours per week for 23 weeks.

The following principles are important factors in generating neuroplastic and thus functional changes in language skills:

1 Massed practice, e.g. 30–35 hours of therapy over 10 days rather than the same therapy time over a longer period;

2 Constraint, in this case of maladaptive methods of communication; and

3 Therapy targets with everyday behavioural relevance;

Overall, an increase in appropriate therapy seems beneficial. Possible cost-effective means of doing this include the use of group training rather than individual therapy, or constraint of the non-affected limb or a conversational partner during waking hours. There are also emerging interventions such as the use of mental imagery, sensory stimulation, an automated robotic (most commonly a treadmill with or without body-weight support for gait training), a virtual environment and the use of tele-rehabilitation to provide therapy within the home, supervised by video link to a centrally located therapist.

Physical therapeutic interventions

In the past 60 years, various physiotherapy treatment approaches have been adopted which have different underlying theoretical assumptions about the control of movement and the mechanisms underlying physiotherapy. Early approaches proposed by Rood, Brunstromm, Knott, Voss and Bobath were initially underpinned by neurophysiological theory, in particular the role of afferent information in facilitating movement. In the last 20 years, theoretical assumptions and knowledge gleaned from biomechanics and motor learning have resulted in the modification of existing approaches and the development of other approaches such as motor re-learning. Currently, in the UK, the Bobath approach tends to be used, while the motor re-learning approach is more commonly used in its country of origin, Australia. The techniques used in these two approaches have many similarities. Both emphasize the need for task-specific practice and the maintainance of muscle length and joint alignment. The motor relearning approach emphasizes time spent practising task-specific activities and strength training, and verbal instructions to direct and correct movement performance. By contrast, the Bobath approach emphasizes the need to facilitate components of normal movement that are absent and to normalize tone. There is a greater use of external manual guidance to guide and correct movement performance. Despite these differences, studies comparing the effectiveness of these and other approaches have revealed no difference in their efficacy. This may be because of the similarities in the techniques, or the fact that therapy only forms a small part of a patient's day.

Physical interventions for hypertonia focus on the non-neural contributions to tone resulting from an increase in the resistance offered by the intramuscular and peri-articular connective tissue and include stretching and splinting techniques. Neural contributions to hypertonia, caused by an increase in stretch reflex evoked muscle activity (spasticity), are amenable to pharmacological interventions. In an individual patient it is important to distinguish as far as possible between the neural and non-neural (soft tissue) contributions to tone, which may vary with time post-lesion. The extent to which an enhancement in stretch evoked activity, spasticity, impairs functional movements remains unclear. Difficulties in tasks such as standing and walking may be predominately caused by the muscle weakness, deficits in selective muscle activation and lack of posturally evoked muscle responses that are also seen in the upper motor neurone syndrome.

Although it is possible to distinguish these components experimentally, clinical tests such as the Tardieu test (which measures range of motion during fast passive movement of a joint) at best only allow an estimate of these components. Physical interventions are likely to influence the enhancement in stretch evoked activity, possibly via inhibitory sensory input resulting from the patient's active movement and positioning, in much the same way as transcutaneous electrical stimulation (TENS) and specific cutaneous nerve stimulation have been shown to inhibit stretch reflexes in people with spasticity, possibly via modulation of presynaptic inhibitory interneurones. However, to date evidence for the role of specific physiotherapeutic handling techniques to decrease spasticity is lacking.

Maintenance and restoration of muscle length and muscle compliance is vital in the management of hypertonia as well as in people with muscle weakness who are unable to voluntarily move their joints through full range. This may be achieved using a variety of techniques including active and passive stretches, standing regimes, casting, orthoses and optimizing sitting posture in a wheelchair. The recommended type and duration of manual stretches remains unclear. Experimental evidence suggests that greater effects on ankle visco-elastic properties are seen post-stroke when a static constant torque (80% of the initial end range torque) is applied, rather than when the limb is held at a constant position or during cyclic stretching. These effects are seen after a period of 30 minutes: shorter periods of stretch and their time course need to be further investigated. Casting of upper and lower limb joints in adults with acquired brain injury can significantly increase passive range of motion and prevent the development of contractures. Casting may also reduce stretch reflex hyperexcitability as measured by a reduction in stretch reflex threshold. Uni- or bi-valving a cast allows its removal for hygiene, therapy and to assess tissue viability. Minor skin breakdown has been reported in up to 66% of cases and resolves spontaneously or with therapeutic dressings in 90% of cases. With serial casting, similar gains in range but fewer complications are seen with shorter periods between recasting (1–4 days versus 5–7 days).

Mental imagery and sensory stimulation techniques can be used to facilitate motor retraining. Mental imagery of an action activates areas of the brain that overlap with those involved in motor control. Imagined motor tasks obey the same constraints as performed actions and have thus been trialled as an adjunct to help the rehabilitation of functional movements. After stroke, improvements in upper limb use have been reported after mental imagery of ADL, and after motor imagery of paretic limb movement in conjunction with movement of the non-paretic limb in a mirror in the same direction and orientation as the imagined movements of the paretic limb.

Visual and auditory cueing, as well as treadmill training, have been used to overcome the freezing, festination and falls of patients with Parkinson's disease and improve gait cadence, stride length and velocity. Six to eight weeks of physiotherapy and exercise training, with or without auditory cueing, improve mobility and independence, but it remains unclear whether the positive effects obtained in these initial studies can be sustained in the longer term.

Sensory facilitation techniques use the application of stimuli such as muscle stretch, tactile input and weight-bearing through the affected limb to achieve muscle activation. Many of these inputs modulate spinal cord circuitry as the effects are seen in paretic muscle of people with complete spinal cord lesions, although supraspinal modulation may occur. These passive sensory stimuli facilitate muscle responses less than voluntary activation and so active participation should be encouraged wherever possible.

Sensory retraining post-stroke may result in similar changes in cortical maps to those that follow a discrete lesion to the primary sensory cortex in primates, when restoration of the central response to stimulation of the hand can be observed over time. Training regimes vary between groups but tend to include a progression from localizing to discriminating different tactile and proprioceptive stimuli, and practice in tasks requiring stereognosis. Improvements in tests such as two-point discrimination have been found in a controlled trial while single case studies have shown that tactile and proprioceptive discriminatory functions may improve with training, and that with specific training regimes improvements may be generalized to other modalities. The effect that these improvements have on functional upper limb tasks has not yet been explored.

Muscle strengthening in the context of muscle weakness is important after both central and peripheral neural damage. Muscle weakness after a CNS lesion is common and is often the result of a primary deficit in central control. Following stroke, a lack of response in hand muscles to TMS over the primary motor cortex is a predictor of poor recovery. A lack of descending control results in alterations in motor unit recruitment, firing patterns and inappropriate agonist–antagonist coactivation. With time, changes in muscle fibre type and alterations in muscle length and the length–tension relationship occur; disuse atrophy may also develop as sensorimotor deficits limit a person's normal level of activity. Muscle weakness in turn predicts poor function. Lower limb weakness, for example, is associated with reduced walking speeds and stair climbing ability post-stroke.

Electrical stimulation can maintain and improve muscle strength in upper and lower limbs but the effects on ADL may be minimal. Most studies have assessed the effects of stimulating distal musculature such as the wrist extensors and tibialis anterior. Electrical stimulation of rotator cuff muscles via intramuscular electrodes for post-stroke shoulder subluxation has repeatable effects on associated shoulder pain and some reports have shown a reduction in the degree of subluxation. Neuromuscular stimulation may also be initiated by electromyography (EMG) signals recorded from the target muscle. This technique may result in larger gains in motor control because active participation optimizes motor relearning and early trials in small groups suggest that EMG triggered stimulation of the wrist extensors results in significant gains in strength as well as improvements on functional scales.

Progressive resisted strength training post-stroke can also result in an increase in upper and lower limb muscle strength without any increase in spasticity. Such strength gains can in turn lead to functional improvements, e.g. in stair climbing and walking. To date the optimal type of exercise protocol for strength training – isometric, concentric, eccentric and open or close-kinetic chain exercises and the resistance and number of repetitions – has not been fully investigated.

Constraint induced movement therapy (CIMT) following stroke or traumatic brain injury (TBI) involves constraining the non-paretic side while performing intensive (forced use) task-oriented therapy on the paretic limb. The constraint is worn for up to 90% of waking hours for 14 days, except for activities requiring balance and water-based activities such as toileting and washing. The training involves general task practice and shaping, a type of part practice whereby the behavioural goal is approached in small steps. Feedback about task performance, often in terms of the time to perform a task or the number of repetitions performed, is given at each step. Studies investigating this approach have shown significant improvements in functional ability and motor impairment in both chronic and acute stroke patients as well as a subjective increase in the amount and quality of functional use of the paretic limb. This led to a pioneering prospective single-blind randomized multi-site study recruiting 222 patients 3–9 months post-stroke over 2 years by Wolf *et al*. Accompanying the reported behavioural changes, alterations in motor maps and movement-related activation patterns assessed using TMS and fMRI have been reported. Inclusion criteria for studies of CIMT require a degree of initial sensorimotor function in the paretic limb. Therefore, the patients who benefit from this approach may potentially represent only 20–25% of the stroke population. The important aspect of CIMT, as well as the hallmark constraint of the non-paretic limb, is the intensive training performed with the affected limb. The time spent training is longer than reported for other approaches, up to 6 hours of practice for 10 out of 14 days and may explain the large effect size, so that one study reported no difference in the degree of motor recovery when this technique was compared with conventional therapy of a similar intensity level. Since 2001, modified CIMT (mCIMT) given over only 30 minutes 3 times a week but for 10 weeks, with constraint of the less affected hand for only 5 hours a day for 5 days, has been reported in a series of small studies by Page and colleagues to produce similar benefits when given to patients late after TBI and either late (several months), subacutely or less than 14 days post-stroke. There was some or, in certain cases, only minimal movement in the affected wrist and fingers, and mCIMT was combined either with botulinum toxin into wrist and finger flexors or with a home-based exercise programme via a computerized video link to a therapist, making mCIMT potentially more attractive to a larger population.

Balance, posture and mobility require the integration of multi-sensory information (visual, vestibular and somato-sensory) at multiple levels of the CNS, and as a result of this distributed control are often affected by neural damage. Postural stability is a vital prerequisite for all functional movements, and without postural stability the limbs are often used to aid balance. Positioning and specialized seating may be required to substitute for impaired mechanisms of postural control and can improve limb function, prevent progression of deformity such as scoliosis and windswept limbs, and to achieve a larger area of pressure distribution, thus preventing pressure sores and associated complications. Compensatory approaches to gait rehabilitation and mobility include the use of walking aids and orthoses. Such interventions do not increase gait asymmetry as previously thought and can reduce energy expenditure. The provision of an appropriate manual or electric wheelchair can also greatly improve mobility.

Targeted training of balance and posture involves initially fixating unstable body segments and retraining the balance of one segment on another. Progression involves reducing the degree of fixation, thus increasing the degrees of freedom that need to be controlled. Specialized fixation systems are available for the paediatric population, while in adults simple techniques such as backslabs to the legs may be used to retrain trunk or pelvis balance. A more complex system using similar principles is the multi-purpose trainer which consists of a hip frame that fits around the pelvis with vertical supports connecting the frame to a base via joints at the level of the ankles. The stiffness of these joints can be varied via actuators which can also provide perturbations to the frame. This allows the individual to retrain balance safely in multiple directions. As they become more able to control multiple segments, the stiffness of the external frame can be reduced.

Treadmill training with body weight support via a harness system allows repetitive practice of the entire act of walking. The task can be progressed by varying the treadmill speed and incline, decreasing the assistance given by the therapist and decreasing the amount of body weight support. This increases balance requirements and the need for antigravity muscle activity. In the context of complete spinal cord injury, treadmill training results in improvements in the timing and amplitude of muscle activity, when lower limb loading seems to be an important stimulus. However, unlike the complete spinal cat, following complete spinal cord injury in humans such training does not result in functional walking, reflecting the need for some descending central control of walking in man. Treadmill training in those with acute and chronic incomplete spinal cord injury can result in improvements in over-ground walking above that seen with conventional therapies. Treadmill training following stroke can improve over-ground gait speed, symmetry and kinematics. The best results seem to be in those who are already walking independently, although favourable results have been reported in patients with acute stroke. In contrast to the effects of treadmill training, no effect on gait asymmetry was seen after a 4-week programme of in-patient rehabilitation based on the Bobath approach. It was suggested that this was because the therapy was not task-specific and concentrated instead on part practice and walking practice at reduced speeds.

Functional electrical stimulation (FES) of a peripheral motor nerve and the muscles supplied may be used to compensate for muscle weakness. One example is the Odstock footdrop stimulator which compensates for the presence of footdrop. Here a heel switch detects the time the heel rises off the ground; this in turn triggers stimulation of the common peroneal nerve via surface electrodes and thus contraction of the tibialis anterior muscle. This results in dorsiflexion during the swing phase and can result in up to a 30% increase in walking speed following stroke. With prolonged use, an increase in walking speeds without the stimulator may also be observed, possibly by increasing muscle strength.

Multi-channel FES has also been used to retrain standing, weight transference and gait. Stimulation may be via surface or subcutaneous electrodes and more recently direct stimulation of the nerves via cuff electrodes. In people with paraplegia a minimum of four channels are required for ambulation when used in combination with a walking aid. Stepping can be induced via common peroneal stimulation resulting in ankle dorsiflexion and a flexor withdrawal reflex, while stimulation of the quadriceps provides knee control during the stance phase. Hand or foot switches are used to trigger alternate leg movements and the person requires sufficient arm strength to provide balance via the walking aid. Multi-channel FES systems have been used in combination with orthoses, providing hybrid assistive systems with greater external symmetry. Reports of people with paraplegia achieving independent stance and gait have been described. However, many use such systems for exercise and the physiological and psychological benefits of standing rather than for functional tasks. Difficulties that remain in making these systems a realistic clinical tool include:

- Muscle fatigue with stimulation that limits the duration of standing;
- The presence of hypertonia, spasms and joint contractures that alter joint torques and thus limit functional movements;
- The high energy cost of walking with such a device; and
- The time taken to don and doff the system.

Difficulties of this sort and unrealistic expectations result in many people discontinuing these systems within a year.

Cardiorespiratory training and exercise classes may reverse the detraining effects of immobility and reduced activity seen in many chronic conditions. Aerobic capacity, measured by peak oxygen consumption on maximal exercise testing, is reduced and this may in turn limit functional tasks. After stroke, exercise capacity is reduced to about 60% of normal at 1 month, making the performance of ADL effortful and fatiguing. Although ADL exert a training effect so that exercise capacity improves, it remains reduced at 6 months and probably long term. Activity intolerance is thus common among stroke survivors who may work close to their individual maximal exercise capacity compared with age- and weight-matched controls while engaged in only domestic chores. Aerobic training, muscle strengthening or both usually improve targeted outcomes including balance and walking speed and distance, although not consistently ADL. Recommendations for exercise after stroke have been made by the American Heart Association. Exercise classes, consisting of aerobic exercise and progressive resisted exercises lasting around 30–40 minutes 1–3 times per week for periods of up to 6 months, may also improve muscle strength, aerobic capacity and mobility in people with mild to moderate multiple sclerosis (Kurtzke Expanded Disability Status Scale <6; Chapter 10) who are not experiencing an exacerbation.

Biofeedback has been used to re-educate standing posture. Patients with hemiplegia post-stroke stand asymmetrically and take less weight on their paretic limb. In the paretic limb there is reduced amplitude or delayed responses following a postural perturbation or accompanying a volitional upper or lower limb movement. Using feedback about weight distribution, e.g. provided by a balance performance monitor, people post-stroke can improve sitting and standing symmetry. However, this has no effect on more dynamic tests of balance or on the degree of symmetry the person shows while walking.

Two emerging technologies, robotics and virtual reality, are likely to provide new opportunities for skill retraining after neural injury and may be used to increase the amount of therapy while allowing therapists to concentrate on task-specific retraining. Robotic devices may be used to provide appropriate assistance or resistance to a movement depending on the person's level of impairment. They have the advantage of being able to control and record movement-associated forces and kinematics, and so the intensity of therapy can be accurately determined instead of simply stating the total duration of therapy. Studies using robotic devices to retrain proximal upper limb movements in stroke have demonstrated significant improvements in motor impairment. Similarly, robotic gait machines are now being used to aid walking rehabilitation in people with stroke and incomplete spinal cord injury. Such devices are equally effective as treadmill training but significantly reduce the need for the therapist to facilitate paretic leg swing and weight transference on to the paretic stance limb.

Virtual reality technology allows the establishment of a virtual two- or three-dimensional visual environment. The display may be head mounted or movement of the head can be used to produce movements of the visual scene as in the real world, and it is also possible to give haptic force feedback from a virtual object via a manipulandum. It is thus possible to create a complex variable environment for intensive retraining of sensorimotor function, factors lacking in many conventional therapy approaches. Upper limb movements in a virtual and a natural environment are similar in both healthy subjects and after stroke, although differences do occur when using a two-dimensional environment. Upper limb training in a virtual environment after stroke has resulted in improvements in motor function that transfers to the natural situation. The ability to manipulate the visual scene is also an advantage for the rehabilitation of balance, particularly in those subjects who have over-relied on visual information to balance while not utilizing remaining vestibular and somato-sensory information, for example after central and peripheral vestibular lesions. The possibility of rehabilitation at a distance from the therapy department, also known as telerehabilitation may increase further the overall intensity and duration of intervention.

Management of neurological impairments

Symptoms related to neurological impairments caused by either single incident or chronic progressive conditions may simply be unpleasant or annoying or may have a highly significant impact on function. Each person's needs therefore differ and their optimal function and well-being will only be attained if individualized treatment goals, functionally relevant to the patient, are defined. This approach facilitates learning and self-management techniques, skills that do not result from generic prescription for a given impairment. This will often involve several different disciplines working across health and social care sectors to enable the individual to incorporate treatment strategies into their daily life and to ensure that interventions take place in an effective and timely fashion.

The impact of spasticity on an individual is extremely variable. It can either be very useful, perhaps allowing an individual to stand or walk when weakness would otherwise not permit it, cause minor discomfort or stiffness, or result in devastating loss of function with development of long-term problems such as pressure sores and contractures. Chronic pain or spasms frequently interfere with sleep; they may impact on mood, self-image or motivation. They can obviously also impact on function so that walking may be slower, falls more frequent, the ability to selfpropel a wheelchair or transfer reduced and many ADL such as washing, dressing, toileting and sexual activity compromised. Any of these problems can have a detrimental affect on the ability of an individual to continue in employment or education and/or impact on fulfilment of other life roles including those as a parent or partner. Poorly managed spasticity can also have serious long-term physical consequences. Muscle shortening and tendon or soft tissue contractures can lead to restriction of passive movement and physical deformity. Once present, contractures may be very difficult to treat and can have major functional implications, causing difficulties with personal hygiene or dressing, problems in positioning and seating and thus restricted community mobility and social isolation. The development of pressure sores may in turn increase spasticity and spasms, to cause a vicious circle of further contractures and dependency. An awareness of these possibilities and early identification and intervention can minimize development of these long-term secondary complications. It is thus imperative that management is always individualized and focused upon function rather than aimed simply at the reduction of spasticity as a sign or symptom.

The mainstay of management is education of the individual and, if applicable, their family or carers in strategies to manage their own spasticity and the implementation of an effective regime of physical therapy including stretching and, if possible, standing with or without assistance. Knowledge of the triggers and aggravating factors detailed in Table 17.3 are particularly important as they can exacerbate spasticity and its associated features. Pharmacological treatment is far too often escalated before appropriate strategies to manage bladder and bowel function, skin integrity, soft tissue length and positioning are instigated. Attention to these simple but essential areas is paramount at all stages of management and will ensure drugs are used at appropriate times and dosages.

Table 17.3 Common cutaneous and visceral stimuli aggravating spasticity.

Cutaneous stimuli	Visceral stimuli
Altered skin integrity	Any systemic or localized infection
Red or inflamed skin	Bowel dysfunction, e.g. constipation, overflow or diarrhoea
Broken skin	Bladder dysfunction, e.g. infections or incomplete emptying
Infected skin	Deep vein thrombosis
Pressure sores	
Ingrown toenails	
Tight fitting clothes or urinary leg bag appliances	
Uncomfortable orthotics or seating	

There is no agreed evidence-based model available for the systematic pharmacological management of spasticity and much of what is done is based on a logical and pragmatic approach. The identification of appropriate treatment goals will help optimize drug therapy in terms of choice of agent but also in timing and dose. For example, painful nocturnal spasms may best be managed with a long-acting agent that has sedative side-effects taken at night-time. Alternatively, stiffness and spasms that interfere with an individual's morning transfers and personal care may benefit from medication taken on waking, prior to transferring out of bed. Dosages for those who are walking and who may rely on their spasticity to do so, are often lower than in those who use a wheelchair for mobility.

The general rule to 'start low and go slow' means that it may take some time to optimize a treatment regime. This approach will limit any deleterious effects on function or unwanted side effects and it is important that drugs are not discarded before the dose reaches the maximum level or side effects occur. All currently available drug treatments for spasticity can have side effects and one should use lowest dose regimen that effectively controls symptoms; the most common problems are drowsiness and weakness which may be caused by unmasking underlying weakness by removing tone, i.e. reducing spasticity which was functionally useful. Despite optimal nursing, physiotherapy and the use of physical adjuncts such as specialist seating systems, it is not always possible to control spasticity with a single drug without causing unacceptable side effects. A combination of agents at lower doses may enable effective treatment with tolerable side effects.

The oral agents most commonly used are baclofen, tizanidine, benzodiazepines, dantrolene and gabapentin; all can be used alone as monotherapy or in combination (Table 17.4). It is also

Table 17.4 Oral antispasticity agents.

Drug	Starting dose	Maximum dose	Side sffects
Baclofen	5–10 mg/day	120 mg/day, usually in 3 divided doses	Drowsiness, weakness, parasthesiae, nausea, vomiting
Tizanidine	2 mg/day	36 mg/day, usually in 3 or 4 divided doses	Drowsiness, weakness, dry mouth, postural hypotension ** Monitor liver function*
Dantrolene	25 mg/day	400 mg/day, usually in 4 divided doses	Anorexia, nausea, vomiting, drowsiness, weakness, dizziness, parasthesiae ** Monitor liver function*
Diazepam	2 mg/day	40–60 mg/day, usually in 3 or 4 divided doses	Drowsiness, reduced attention, memory impairment ** Dependency and withdrawal syndromes*
Clonazepam	0.25–0.5 mg, usually at night-time	3 mg, usually in 3 divided doses	Same as diazepam
Gabapentin	300 mg/day (can start at 100 mg/day)	2400 mg/day, usually in 3 divided doses	Drowsiness, somnolence, dizziness
Cannabis and cannabinoids (e.g. Sativex)			

possible to combine oral therapy with local or regional treatments such as botulinum toxin, focal chemical neurolysis or intrathecal therapies including baclofen and phenol. Most of the clinical trials of baclofen and tizanidine in the management of spasticity have involved patients with either multiple sclerosis (MS) or spinal cord injury. Few have concentrated on spasticity of cerebral origin, although one placebo-controlled trial of baclofen in stroke has shown a beneficial effect on the Ashworth score (spasticity rating) and overall evaluation but no change in the Incapacity Status Scale. Two studies in stroke revealed a reduction in tone and spasms with tizanidine compared with placebo. No difference in efficacy or tolerability was seen in a comparison study between baclofen and tizanidine in a stroke population. Although most studies have shown a positive effect of baclofen or tizanidine in reducing hypertonia and spasms, little attention has been paid to functional benefit. Four small double-blind placebo-controlled randomized studies of gabapentin have been performed to date. Two of these were in MS patients, one was in spinal cord injury alone and another included patients with any cause of upper motor neurone syndrome. All showed a beneficial effect for gabapentin on measures of spasticity without excessive side effects.

With the exception of tizanidine and dantrolene, these drugs act by potentiating the action of the inhibitory neurotransmitter GABA. Tizanidine is predominantly an α_2-agonist and thus decreases presynaptic activity of the excitatory interneurones. Dantrolene is the only antispasticity treatment that acts primarily on muscle by inhibiting calcium release from the sarcoplasmic reticulum which decreases the excitation–coupling reaction involved in muscle contraction. Cannabis has been used by individuals with MS for many years on the basis of anecdotal evidence. Synthetic cannabinoids, e.g. Sativex, are now available. Two large recent studies did not show a change in the Ashworth score. Although both suggested a subjective improvement in symptoms, there was some patient unmasking in the active treatment groups. Further trials are anticipated to clarify effect, particularly in functional areas.

Botulinum toxin (BTX) type A, but not type B, is the most widely used focal treatment for spasticity. The toxin irreversibly inhibits release of acetylcholine at the neuromuscular junction but its clinical effect is reversible because nerve sprouting and reinnervation leads to functional recovery of the muscle over a few months. The toxin is injected directly into the targeted muscle and takes 10–14 days to have a visible effect. Treatment may have to be repeated after a several months. It is essential that BTX injections are followed by goal-focused physiotherapy to obtain the maximum benefit. Because spasticity does not contribute significantly to impairment during active voluntary movement and function in either the leg or arm, even good trial design and the inclusion of functional outcome measures shows that BTX benefits passive rather than active functional activities. These include hand movement and perineal hygiene, dressing, pain and limb position. Correction of equino-varus at the ankle to improve weight-bearing by the affected leg is unlikely to translate into functional improvements in gait unless it is followed by physical measures to reduce soft tissue shortening and a program of task-related training. There is only limited information about the long-term efficacy of repeated treatment cycles with BTX. Two open label studies of 3–4 treatment cycles of BTX at 12–16 week intervals in patients with post-stroke upper limb spasticity have shown no reduction in effect of the toxin over time; only one patient developed neutralizing antibodies. Local injection of ethyl alcohol or, more commonly, phenol is an alternative option to BTX for focal management of spasticity. Chemical neurolysis is irreversible and results in destruction of neural tissue by protein coagulation. Injections may be targeted at peripheral nerves or motor points, areas of muscle most sensitive to electrical stimulation. Partial nerve regeneration and sprouting may subsequently occur so that the clinical effect may wane after several weeks or months. If necessary the injections can be repeated. Those most commonly applied are medial popliteal blocks to aid spastic foot drop, or obturator nerve blocks either in ambulatory patients with scissoring gait or with the aim of improving ease of perineal hygiene and seating posture.

If oral medication in combination with appropriate physical measures is not tolerated or fails to control lower limb spasticity, e.g. to enable safe seating or hoisted transfers, then intrathecal delivery of baclofen should be considered. The concentration of GABA receptors in the lumbar spinal cord allows very small dosages of intrathecal baclofen to be effective without causing any systemic side effects. Intrathecal baclofen has been shown to be an effective treatment option in the management of severe spasticity of either cerebral or spinal origin. A programmable pump is implanted into the abdomen and a catheter conveys the baclofen into the intrathecal space. Intrathecal phenol and very occasionally posterior rhizotomy can also be effective treatments; they require expert administration but do not have the long-term maintenance and cost problems that go with intrathecal baclofen treatment. Because phenol is a destructive agent that indiscriminately damages motor and sensory nerves, it is reserved for those individuals who have no functional movement in their legs, who have lost bladder and bowel function and who have impaired sensation to their legs. The effect of a single injection often lasts many months and can be repeated if necessary.

Cerebellar ataxia is an extremely challenging symptom to manage. The effects on the individual are variable and may cause only minor problems with finger dexterity in some patients but in others catastrophic loss of upper limb function, mobility and even loss of sitting balance. Severe tremor and head titubation may occur in severe cases and can be very distressing for the patient. Physiotherapy and occupational therapy are the mainstay of management. By optimizing the individual's seating position, posture and the provision of distal supportive aids, the ease and quality of functional tasks such as feeding, self-care and keyboard use can be improved. Drug therapy is of limited value because of poor efficacy and adverse affects, but isoniazid in combination with pyridoxine is occasionally of help to some patients. Other drugs that are often tried with variable success include clonazepam, carbamazepine, mirtazepine and propranolol.

Ondansetron, a 5-HT_3 antagonist, has been reported to be effective in a small pilot study of patients with severe cerebellar tremor and was well tolerated, the main side effects being headache and constipation. This modest effect has been confirmed for both tremor and vertigo. Cannabinoids and whole plant cannabis extract, despite being advocated by many individuals with MS, have failed to show a benefit for tremor in treatment trials.

For severe cases it may be appropriate to consider neurosurgery. In the past this was commonly ablative surgery performed stereotactically and targeting the ventrolateral nucleus of the thalamus. More recently electrostimulation, usually of the ventro-interomedial nucleus of the thalamus, appears to be more beneficial and less hazardous, with nearly 90% of patients reported to experience at least some sustained improvement in tremor control. Effects on function have been less consistently reported, and preoperative patient education about what functional changes are realistically likely to occur is extremely important. Side effects include hemiplegia and dysphagia. Although a potentially useful technique, complete cessation of tremor is rarely achieved and frequent reprogramming may be necessary.

Pain is unfortunately very common in neurological conditions and can be very debilitating for the individual, interfering with mobility and sleep and contributing to depression. It may be neurogenic in origin or secondary to mechanical factors brought about by spasticity, weakness and immobility. Back pain is particularly common in wheelchair users, in whom spasticity, immobility, abnormal posturing and often an extremely effortful and abnormal gait affect the paravertebral musculature and lumbar spine. This exacerbates degenerative disease. Early physiotherapy is essential to aid in spasticity management, to correct posture and/or gait and to limit further damage. Pain relief should include local measures such as heat pads and TENS. Medication may be necessary and includes short-term use of non-steroidal anti-inflammatory drugs and simple analgesia. During the first 6 months after stroke, shoulder pain occurs in over 60% of patients and may increase in incidence after discharge. It causes considerable morbidity and once established is difficult to treat. Its occurrence correlates with pre-stroke shoulder pain, severe upper limb weakness, neglect, sensory loss, visual field defects and gleno-humeral subluxation, but their role in its pathogenesis remains uncertain and shoulder subluxation is not clearly a cause. Autonomic changes in the limb, shoulder–hand syndrome and reflex sympathetic dystrophy may also be seen but should not be confused with the painful shoulder. Other disorders of the shoulder including fractures should be excluded. Prevention, particularly in patients at high risk, should include support of the flaccid arm and appropriate handling techniques to avoid traction injury. Treatment is likely to be partly determined by the tone in shoulder muscles. A flaccid shoulder requires support at all times and possibly benefits from FES; a spastic shoulder requires maintainance of range of movement by physical techniques and possibly botulinum toxin injection. Local steroid injection should be avoided unless there is clear evidence of an inflammatory component to the pain.

Neurogenic pain results from injury to peripheral or central afferent pathways. Its characteristics and management are summarized elsewhere (Chapter 22). It is seen in 60–70% of patients with spinal cord damage, usually traumatic in origin, when it is treated in the same way as central pain following stroke or other brain injury. If refractory, patients may be considered for spinal or deep brain stimulation. Pain is reported in 28–86% of patients with MS. Most have chronic pain but an estimated 10% have acute paroxysmal pains, the most common of which is trigeminal neuralgia which occurs much more often in MS patients than in the general population. It usually responds well to carbamazepine or gabapentin. Other paroxysmal pains also occur in MS and include dysaesthetic burning pains precipitated by touch, movement or hyperventilation, sometimes with painful tonic seizures, which may be helped by carbamazepine, gabapentin or lamotrigine.

Central post-stroke pain (CPSP) is reported to develop in about 8% of stroke patients, and is moderate to severe in 5% of patients. Usually, individuals present with CPSP within 1–2 months after a stroke, but occasionally it may be as long as 1–6 years after injury. Symptoms may be vague and hard to characterize, making an early diagnosis difficult. Failure to make the diagnosis can cause prolonged suffering and reduce the potential for successful rehabilitation. The pathophysiology is thought to involve altered somato-sensory processing at thalamic and cortical levels. The clinical features are extremely varied and include muscular sensations, dysaesthesias, hyperpathia, allodynia, shooting pains or visceral pain such as bloating or fullness of the bladder. Treatment is similarly varied and may include opioids, tricyclic antidepressants, anticonvulsants and even intravenous lidocaine.

Bladder and bowel dysfunction, when not caused by autonomic neuropathies (typically diabetic), medications causing bladder/bowel hyporeflexia, pre-existing bladder outflow obstruction in men or stress incontinence in women, are extremely common in neurological conditions, particularly when there is spinal cord damage (Chapters 15 and 24.) In MS, estimates of bladder dysfunction are of the order of 75% and bowel dysfunction approximately 50%. Common bladder symptoms are those of frequency, urgency and nocturia. As bladder dysfunction increases, incontinence, retention and urinary tract infections occur. Most of these are a result of a combination of detrusor hyper-reflexia causing urgency and incontinence and sphincter dyssynergia causing failure to empty and thus increased residual volumes. As urinary symptoms are often of mixed aetiology it is essential to assess bladder emptying by measuring the post-micturition residual volume, by either catheterization or preferably trans-abdominal ultrasound, before initiating any therapy. If there is no residual volume, then detrusor hyper-reflexia can be treated with anticholinergic agents such as oxybutynin or tolterodine. If nocturia fails to be controlled with anticholinergics, the use of desmopressin (DDAVP) delivered by a nasal spray can be considered, although caution must be taken to avoid overdose and potentially dangerous hyponatraemia. Other potential agents to reduce detrusor hyper-reflexia include intravesical capsaicin or botulinum toxin type A. Detrusor–sphincter dyssynergia can be treated using clean intermittent self-catheterization (CISC). Often, patients require a combination of CISC and an anticholinergic but bladder control is usually greatly improved. Occasionally, control remains poor and an indwelling catheter needs to be considered. In the long term, a suprapubic catheter is usually preferred.

Urinary incontinence after brain damage, for example after-stroke or head injury, is usually the result of disruption of the suprapontine inhibition of bladder contractility, causing detrusor hyper-reflexia. However, detrusor hyporeflexia and retention may occur after damage to the micturition centre in the dorsolateral pons. Occasionally, frontal lobe damage causes inability to suppress the urge to void (a frontal function in health) leading to uninhibited sphincter relaxation. To these difficulties may be added functional incontinence caused by cognitive and communication difficulties and mobility problems. Evidence for the effectiveness of methods promoting continence after brain damage is currently derived largely from trials in other patient groups and after exclusion of outflow obstruction, which may be the result of stricture caused by previous catheter traction in acutely agitated patients. Management often includes a combination of specialist assessment, anticholinergic drug therapy and behavioural management, more commonly used in residential settings for elderly or demented people, by prompted and/or timed voiding.

Bowel dysfunction is less frequent than urinary dysfunction in the context of MS or stroke but can be extremely distressing and may occasionally result in bowel perforation or lead to pseudo-obstruction. Usually, individuals complain of constipation and urgency; incontinence is less frequent. Management of constipation is easier than incontinence and after stroke may be helped by avoiding the use of constipating anticholinergic drugs, improving toilet access and education. The establishment of a routine is probably important. Often treatment with oral agents including lactulose, senna or Movicol used regularly is enough but glycerine suppositories and micro-enemas can be extremely useful. Incontinence often linked to urgency can be helped with loperamide.

Sexual dysfunction is a problem often overlooked by health professionals but is extremely common in neurological disorders, usually with accompanying bladder dysfunction. Hyposexual behaviours are most commonly reported after stroke and TBI, and in the context of Parkinson's disease and MS, in which the incidence of erectile dysfunction is in the order of 70%. Psychological factors in either patient or partner may play a part. Psychosexual counselling should be considered in all cases alone or in combination with other therapies. The advent of the phosphodiesterase-5 inhibitors such as sildenafil, tadalafil and vardenafil which are fast-acting oral drugs have reduced the need for more invasive techniques such as intracavernosal injection of alprostadil (prostaglandin E_1). Women complain most frequently of vaginal dryness and of difficulty reaching orgasm. The use of lubricating gels may be helpful and there is some evidence that sildenafil may help some women although the response is less clear than in men.

Fatigue is particularly problematic for individuals with MS and is well recognized after TBI or stroke. Patient-derived stroke-specific health-related quality of life (QoL) measures identify lack of energy as one of the four most impacting problem areas following stroke. If severe, fatigue may limit education, employment and social opportunities. Its occurence following stroke is predicted by pre-stroke fatigue and the degree of dependence and depression post-stroke, but it occurs independently in some patients as primary post-stroke fatigue, possibly resulting from stroke-disordered attention either in association with physical impairment, sleep-disordered breathing and obstructive sleep apnoea or incidental systemic co-morbidities. Management clearly starts with accurate differential diagnosis, but there are neither guidelines to advise management of primary post-stroke fatigue nor evidence that modafinil really helps. Initial therapy for all causes of fatigue should be aimed at optimizing sleep pattern, e.g. treating nocturnal spasms, nocturia or depression and instigating a personalized fatigue management programme. Occupational therapists can be of help in devising such programmes, which include looking at the individual's daily routine to incorporate fatigue-limiting strategies and introducing regular rest periods. In MS, amantadine has been shown in small studies to be of some benefit. CNS stimulants such as pemoline are best avoided because of side effects and dependency. Other agents such as 3,4-diaminopyridine have been investigated but side effects limit routine clinical use.

Visual dysfunction can result from conditions affecting any part of the visual pathway from the retina to the occipital cortex or oculomotor connections in the brainstem. Symptoms include loss of acuity, field defects, diplopia or oscillopsia. Poor recovery from optic neuritis, or occasionally progressive optic neuritis, are the most common cause of visual problems in MS, although diplopia and oscillopsia can also be extremely disabling. Patients with optic nerve dysfunction may be helped by referral to low vision clinics. The management of nystagmus and oscillopsia is extremely difficult; converging prisms may be of use and several drugs have been reported to help in small cohorts of patients: baclofen, valproic acid, trihexyphenidyl, clonazepam, isoniazid, gabapentin and 3,4-diaminopyridine. Botulinum toxin injections may be of benefit in severe long-standing oscillopsia.

Homonymous visual field defects are one of the most common visual sequelae of stroke. These impact on a person's ability to read, drive and navigate within their environment. Rehabilitation strategies to optimize visual function include the use of appropriate aids or visual training. Aids can help by either redirecting the image to a functioning part of the visual field, e.g. by using mirrors, or by expanding the visual field through the use of prisms. Training in a home-based computerized visual search task that improves visual scanning appears to translate into improvements in ADL. Visual training incorporates the concept of blindsight, sometimes present in people with homonymous visual field defects who are able to discriminate visual targets presented to their blind hemifields in a forced choice context. Repeated training may improve this capability.

Dysarthria may occur in isolation, but in the context of brainstem disease or bilateral or extensive unilateral upper motor neurone injury it is often accompanied by swallowing difficulties. Training techniques aim to improve intelligibility by advice about altering articulation, speed, phonation and prosodic voice quality and by increasing orofacial muscle strength and coordination with attention to respiratory support through appropriate exercises. There is little formal evidence of efficacy of these manoevres. Often patients can continue to communicate effectively with friends or relatives who have become accustomed to their speech, but when dysarthria is very severe the use of communication aids can be explored with the therapist.

The effective management of dysphagia, to prevent its attendant and sometimes life-threatening risks of dehydration, malnutrition, aspiration and chest infections in the context of single incident or deteriorating neurological conditions, is difficult to over-emphasize. It occurs clinically in about 50% of all stroke patients admitted to hospital, with video-fluoroscopic and instrumental evidence of a swallowing abnormality in some 80% of patients. Aspiration, particularly silently, predicts chest infection. Video-fluoroscopic and flexible endoscopic evaluation of swallowing increase the reliability with which aspiration can be identified after brain injury of any sort when selecting which patients need tube feeding. After stroke, the FOOD trials in 859 stroke patients randomized to nasogastric feeding within 1 week versus more than 1 week post-stroke found that absolute mortality was reduced by 5.8% in the early group. Percutaneous endoscopic gastrostomy (PEG) feeding was associated with an absolute increase in risk of death of 1.0% and an increased risk of death or poor outcome of 7.8% in 321 patients randomized to PEG versus nasogastric tube a median of 1 week post-stroke. Thus, nasogastric feeding should be used for dysphagic patients early post-stroke, although it may not prevent chest infections, while PEG feeding is reserved for patients in whom nasogastric feeding is not tolerated or is required in the longer term. Non-invasive swallowing therapies in adults with neurogenic dysphagia, using modification of posture or the consistency of food and fluid, oral motor exercises, sensory stimulation, or a combination of techniques may reduce aspiration on clinical testing. However, there is still no robust evidence to show that these therapies reduce the incidence of chest infections or improve nutritional status in the context of either single incident or deteriorating neurological conditions.

The importance of cognitive dysfunction in determining outcome after diffuse single incident vascular and TBI is well recognized and has also been identified after focal stroke, particularly neglect after first-ever stroke and executive dysfunction after any stroke. Its impact on psychosocial function in Parkinson's disease and in MS, when it is unrelated to disease duration or the level of physical disability and prevalence is of the order of 60% in hospital-based studies and 40% in the community, is substantial. Formal assessment of cognitive dysfunction is crucial to realistic goal-planning during rehabilitation, and to the prescription of specific cognitive and behavioural interventions and longer term community-based and vocational rehabilitation and care needs.

Focal language and visuo-spatial disorders are typically seen after stroke or penetrating head injury and both are heterogenous. Neglect, for example, results from different combinations of lateralized and non-lateralized attentional deficits in each patient. A number of techniques have been shown to improve lateralized spatial representation including caloric stimulation, contralesional neck muscle vibration, prism adaptation and contralesional limb activation. Non-lateralized loss of attentional capacity is improved by alerting techniques and drug therapies. Some of these techniques have also been reported to improve ADL. In one notable study, neck muscle vibration with scanning training, prism adaptation and contralesional limb activation reduced length of stay by 24 days. Whether treatment tailored to the neglect or dysphasic subtypes present in each patient will prove sufficiently practical and robust to produce significant functional benefits remains to be explored.

By contrast, more diffuse injury, whether the result of diffuse axonal injury after head injury or a chronic condition such as MS, predominantly affects frontal and subcortical systems with the main deficits involving working memory, attention and executive functions as well as speed of information processing. Treatments demonstrating effectiveness in small Class I studies focus on compensatory rather than restorative strategies for attentional, memory and executive difficulties, usually after TBI. There is a particular need for further trials of comprehensive programmes that address cognitive, emotional, motivational and interpersonal problems that are well documented to have a devastating impact on psychosocial functioning whatever the cause.

There is a high cumulative incidence of psychiatric disorder in the context of any physical illness, predicted by physical and social inactivity and a premorbid history of depression and mental disorder. This holds true for neurological disorders, when additional factors relating to lesion location may play a part, for example left anterior damage affecting frontal–subcortical circuits resulting from stroke, head injury and MS predisposing to depression. Disordered mood may be complicated after brain injury by organic cognitive and behavioural problems and can be difficult to diagnose in the presence of a language disturbance or anosognosia, abulia or confused agitation. Often the behavioural, cognitive and vegetative consequences of anxiety disorders, depression, irritability and pathological emotionalism resolve, but they may impact on compliance and progress in rehabilitation sufficiently to require specific assessment and treatment.

Depression after stroke is probably under-recognized and undertreated. In one recent meta-analysis the frequency in 51 studies was 29–36% with a mean of 33%. In the majority of patients depression resolved spontaneously within a few months. The main predictors for its development are premorbid vulnerability and stroke severity measured by physical disability and cognitive impairment. Its presence predicts increased mortality and resource utilization. Early treatment of depression has been reported to benefit functional outcomes, although a recent systematic review found only modest evidence of benefit from early prevention, diagnosis and treatment.

There is an increased risk, even in the very long term, of a number of psychiatric disorders after mild, moderate and severe TBI. Major depression occurs in about 15% of patients after mild head injury and about one-third of patients after moderate and severe TBI when it is predicted by pre-injury educational or employment difficulties, psychiatric illness, alcohol and substance abuse. The risk of anxiety disorders including obsessive-compulsive, panic and post-traumatic stress disorders is also increased. Psychosis and suicide are more common in people who have had a TBI than in the general population but usually occur in individuals who were vulnerable to these problems pre-injury. Drug treatment with a selective serotonin re-uptake inhibitor (SSRI), sometimes combined with a mood regulator such as carbamazepine for accompanying anxiety disorders, may be useful but should take into account the increased susceptibility to drug side effects of TBI patients. Cognitive behavioural therapy reduced anxiety and depression up to 5 years after mild and moderate injury in a small randomized waiting-listed controlled study. Although cognitive and psychotherapeutic interventions are advocated after severe TBI, rigorous evidence for their efficacy is lacking to date.

Patients with MS may also develop mood disorders or other psychiatric symptoms. These are usually mild and commonly include low mood, irritability, poor concentration and anxiety. Rates of depression in community samples have ranged between 25 and 41% and tend to be higher in nursing home settings. Psychological support or cognitive–behavioural therapy is often all that is required. If medication is indicated it should be used as it is in the healthy population but with greater attention to possible adverse effects, particularly exacerbation of bladder or sexual dysfunction.

Organizational behaviours and outcome measurement

Delivery of organized multi-disciplinary services of any sort demands definition not only of structure, as plant and personnel, but also process. The British Society of Rehabilitation Medicine has proposed clinical standards for in-patient and out-patient specialist rehabilitation services in the UK. These identify the following key elements in the process of rehabilitation, similar to those that drive many complex processes in different arenas:

- Inter-disciplinary assessment and problem definition;
- Treatment planning and delivery;
- Evaluation of effectiveness and reassessment.

An interdisciplinary rehabilitation assessment is very different from that offered by a physician working independently. Patients with complex disability, when multiple factors affecting functional performance present as a single problem, benefit from comprehensive assessment by a rehabilitation team. These teams can work in different ways depending on the setting and on the needs of an individual. Multi-disciplinary working describes a group of different professionals working alongside one another towards a common overall long-term aim, different disciplines delivering interventions to achieve goals in parallel rather than in close collaboration. A more integrated approach is offered by an interdisciplinary team that works together to achieve a series of agreed goals toward a long-term aim. Team members have a fuller understanding of each other's roles and skills and work together in a holistic way, ensuring that different interventions complement each other. This approach is often seen in settings where staff are in geographical contact on a regular basis, either in in-patient rehabilitation units or in the community.

The advantages of an interdisciplinary assessment are that different disciplines identify different contributing problems and can develop an appropriately ordered plan to deal with these contributing causes. For example, a patient with MS may present with a small sacral pressure sore. The contributing factors include immobility, incontinence, undernutrition, lack of insight and motivation, low mood and spasms. The spasms may be aggravated by constipation and incomplete bladder emptying, as well as pain caused by the pressure sore; the tone problems can be ameliorated by seating the patient correctly; the provision of a pressure-relieving cushion may counter the impact of immobility; and CBT or an antidepressant may help depression. This analysis of the problems demands nursing, psychology, medical, occupational therapy and physiotherapy input. Interdisciplinary teams provide a more accurate assessment and decrease the need for hospital admission.

When a team of different disciplines work together they need a structure for assessment and description of an individual's abilities and difficulties. The International Classification of Function (ICF) provides such a structure. It classifies functioning at the level of body or body part, whole person, and whole person in a social context. Disabilities, formerly termed disablements, are:

- Losses or abnormalities of bodily function and structure (impairments);
- Limitations of activities (previously disabilities); and
- Restrictions in participation (formerly termed handicaps).

A person's disabilities and their level of functioning are outcomes of multiple interactions between health conditions and contextual factors. Two sorts of contextual factors are identified:

1 Social and physical environmental factors (e.g. social attitudes, access to buildings, social attitudes, legal protection); and
2 Personal factors which include gender, age, other health conditions, social background, education, overall behaviour pattern and other factors that influence how disability is experienced by the individual.

These interactions help explain why apparently similar patients have different outcomes. An individual patient may complain of difficulty walking, and not only the causes but also the consequences of the problem are likely to differ in different individuals.

Having completed an interdisciplinary assessment and identified the individual's capabilities, disabilities and priorities, the next step is to devise a treatment plan. This treatment plan is usually articulated as a treatment goal. Goal setting may therefore be regarded as a key skill for rehabilitation professionals, although a similar approach is used by other disciplines involved in complex interventions. There is a small but growing clinical literature on the subject of goal-setting but the evidence base for goal-setting was originally derived from the organizational psychology literature of the 1970s.

Locke and Latham recently (2002) synthesized studies of over 40,000 participants and 100 different tasks in eight countries and in field, laboratory and simulated settings into a theory of goal-setting. They define a goal core, mechanisms, moderators and other factors. The goal core defines the task, the level of difficulty and specifics of how, and in what timeframe, the goal should be completed. In other words, goals need to be formulated to be SMART – specific, measurable, achievable, relevant, time-limited. Goals affect performance through a number of mechanisms including directing attention and effort toward goal-related activities and increasing effort and persistence. Challenging goals have been demonstrated to lead to greater effort than low-level goals. The benefits of goal-setting can be moderated by factors such as the individual's commitment to the goal, the importance of the goal to them, their belief that the goal can be attained (self-efficacy), the extent of feedback about goal progress and performance, and the complexity of the task. Thus, the final outcome of goal-setting will depend on the balance between these mechanisms and moderators. Other factors that are important are an individual's willingness to engage with the goal-setting process and their satisfaction with the process. Thus, when considering the specifics of goal-setting it is important to recognize a number of other factors including the importance of the individual's relationships and their previous experience of health service professionals, the impact of the disease itself, particularly in relation to prognosis and disease course, and the views of their family.

Recently, a number of studies of goal-setting in the rehabilitation environment have been reported. Some studies have suggested that people with disabilities and particularly those with TBI should be allocated goals and treatment interventions. In one randomized control trial of 16 adults with TBI, the experimental group were actively involved to a high level in the goal-setting process, by prioritizing wooden blocks which had activities of daily living written on them. In contrast, the controls were involved at a low level. Although both groups initially improved in goal attainment (as measured by Goal Attainment Scaling), at the assessment 2 months following discharge, those experiencing the higher level of involvement had maintained their therapeutic gains in contrast to the low involvement group, who had returned to pretest level.

The part played by goal difficulty and goal origin (self-set goals versus assigned goals) on the performance of brain-injured adults has been assessed in a simple arithmetical task. Eighty-seven patients with a diagnosis of stroke or TBI were randomly assigned to one of three groups: a specific high goal was assigned; a 'do your best' goal was given; or a personal goal had to be stated. Results showed that assigned difficult goals led to better performance than assigned easy goals, and that self-setting a goal did not increase performance to the same level as the assignment of a difficult goal. These findings suggest that goal origin (assigned or self-set), and goal difficulty are important moderators in the goal-setting process and influence performance.

Recently, the association between participation in goal-specific out-patient occupational therapy and improvement in self-identified goals in adults with brain injury has been investigated. Using a repeated measures design, standard therapy designed to achieve specific goals was followed by a period of no treatment. Thirty-one participants with brain injury were recruited at three sites located in different regions of the USA. Participants completed the Canadian Occupational Performance Measure (COPM) and the Community Integration Questionnaire (CIQ) at admission, discharge and 1 and 18 weeks after discharge. In addition Goal Attainment Scales were developed at admission and scored on discharge. Of the 149 goals identified by participants, 81% were achieved. Goal Attainment Scores improved significantly ($z = 7.52$; $P < 0.001$), with a large effect size ($r = 0.94$). The COPM scales showed significantly greater gains during the treatment (average 15.3 weeks) compared to the no treatment period (average 9.9 weeks). It was concluded that participation in goal-specific out-patient occupational therapy that focuses on teaching compensatory strategies was strongly associated with achievement of self-identified goals and reduction of disability in adults with mild to moderate brain injury. However, these results may not be generalizable to the broader brain-injured population.

In summary, clinical studies support the findings of earlier organizational psychology studies that goal-setting has a positive impact on performance and functional outcomes, and that increasing patient participation in the goal-setting process has a positive impact on the generation and achievement of goals. It should not be forgotten that action plans or tasks that have to be undertaken by the multi-disciplinary team underpin the achievement of many goals. Thus, the person with Parkinson's disease may be able to learn over three therapy sessions how to perform a specific task, and potentially could change in 3 days, but if the therapists concerned cannot provide three therapy sessions in 3 days then the goal must allow for this. Similarly, if they can learn how to do a particular task but this is dependent on the ordering and delivery of a piece of equipment, then that need must be recognized, articulated and allowed for.

Research suggests that therapists have been slow to adopt new formalized methods of goal-setting in clinical practice and that many therapists use informal interviews from which vague non-specific goals are generated. While recognizing that the prediction of outcome may be difficult in rehabilitation, non-specific goals

Table 17.5 Goal-based outcome measures.

Outcome measure	Author	Date	Description
Self Identified Goals Assessment (SIGA)	Melville & Nelson	2001	Developed from research in older people, this is designed for occupational therapists to use with clients in subacute rehabilitation and nursing homes. It is the only goal-based outcome measure that provides a protocol to elicit patient identified goals, based on an exploratory interview. Each goal is assigned a rating 0 (unable to do) – 10 (can do) on a visual analogue scale. Post-therapy intervention the patient rates their performance and change scores are compared
Goal Attainment Scaling (GAS)	Kirusek *et al.*	1994	A five-point scale. The expected outcome (goal) is assigned the position of zero on the scale. Better than expected and much better than expected levels of outcome are +1 and +2, respectively. Worse and much worse than expected are −1 and −2. A high level of skill needed on part of the therapist to quantify various levels of goal achievement. This has been used in a variety of settings, demonstrating acceptable inter-rater reliability and concurrent validity (Emmerson & Neely 1988)
Canadian Occupational Performance Measure (COPM)	Baptiste *et al.*	1993	Designed for occupational therapists to use with clients to set goals. Standardized instrument with semi-structured interview format that elicits patient identified goals and quantitative patient ratings of these goals. Change scores between assessment and reassessment are the most meaningful scores derived from this assessment
Self Assessment of Occupational Functioning (SAOF)	Baron & Curtin	1990	Based on the Model of Human Occupation (Kielhofner 1995) which promotes collaborative treatment planning between patient and occupational therapist. This instrument elicits written responses to predetermined items
Satisfaction with Performance Questionnaire	Yerxa & Baum	1986	Quantitative scale of satisfaction with performance in daily occupations and community living. The scores highlight areas of decreased satisfaction with performance. Goals are negotiated between the therapist and patient on that basis

may result in a failure to set boundaries. The setting of vague aims, which lack time limits, is likely to result in suboptimal expectations and performance by the patient and stagnation in the development of skills in the therapist. In response to this need for goals to be specific and measurable, a variety of goal-based outcome measures have been developed (Table 17.5). Of note, apart from the Self Identified Goals Assessment, none of the measures provide theoretical or clinical guidance about how to set goals.

Outcome evaluation of the success of any rehabilitation can examine process or functional outcomes. At the simplest level, achieving a specified goal is a measure of outcome. The difficulty of using goals as outcome measures is that because they are unique to an individual patient they cannot be used to describe groups or compare outcomes between groups. Where suitable outcome measures exist, and are appropriate to both the disorder and the intervention, it may be preferable to examine other outcomes.

Traditionally, physicians have used measures to tell them something about the presence, natural history and severity of a disease. Direct measurement of the extent of the pathology is often impossible, but often there are markers of the disease activity, e.g. MRI changes in MS or [^{18}F]dopa positron emission tomography (PET) in Parkinson's disease. There is now increasing interest in patient-based outcomes that focus on the aspects of health considered important by the patient. These measures typically focus on health-related quality of life. Rating scales measure either generic aspects of health or focus on one particular aspect. Generic measures, such as the M0S SF36 health status scale, allow different patient populations to be compared and allow the inclusion of a control population in a study. Typically, the usefulness of such scales may be limited by their inability to capture a range of outcomes relevant to the particular patient populations studied, and so they may be unresponsive to change in a clinical condition. Alternatives include disease-specific measures such as the Parkinson's Disease Questionnaire-39 (PDQ-39) or the Multiple Sclerosis Impact Scale (MSIS); site-specific scales such as the Disabilities of the Arm, Shoulder and Hand (DASH) outcome questionnaire; or dimension-specific measures which measure one aspect of quality of life such as well-being, e.g. the General Health Questionnaire (GHQ).

Clinically useful instruments should be easy to administer and brief, cheap and easy to analyse, appropriate and measure the outcome that is relevant to the intervention and to that disease group. They should also be acceptable to patients, being neither intrusive nor upsetting. Since about 1990 there has been a marked increase in the numbers of papers that address outcome. Typically, these papers report a new or previously described scale in terms of its psychometric properties. Traditional psychometric approaches inform users about the scientific properties of the scales. Scientifically sound instruments are valid, reliable and responsive. A valid instrument measures what it is intended to measure. Validity cannot be proven but evidence in support of validity can be gathered. Content validity is the extent to which the measure represents the full range of the conceptual domain it addresses. Criterion-related validity compares the measure against a gold standard. Construct validity compares the measure in different situations. Does it correlate with other measures of related entities (convergent validity)? Does it fail to correlate with measures that purport to measure a different concept (discriminant validity)? Does it detect differences in groups known to be different in the concept measured?

A reliable instrument performs in an accurate, consistent and reproducible manner that is stable over time. The purpose of reliability testing is to determine the extent to which random error is present in the measurement. To be reliable, scales need clear descriptions of the meaning of individual points on the scale. There is evidence that idiosyncrasies of performance represent a major source of variability in rating scales. Stability of the scale over time is assessed using test–retest reliability. Inter-rater reliability is the agreement between two or more raters, intra-rater reliability is the agreement between two ratings made at different times by a single observer on the same patients. Responsiveness describes the ability of the scale to measure clinically relevant change, such as the impact of rehabilitation, or the effect of a new drug.

There is now a range of measures used commonly in rehabilitation. The Barthel Index (BI) is the most commonly used assessment of limitations in personal ADL. It consists of 10 items measured on either a two, three or four point scale, with a maximum score of 20. The BI has been well studied in a number of settings and its general validity has been established. It correlates well with clinical impression, with motor loss after stroke and with scores on other ADL scales. It is reliable and simple to use but its content is only relevant to people with moderate and severe disability. However, despite being widely used and having been evaluated using traditional psychometric approaches, it is clear that there remain a number of problems. First, the Barthel is an ordinal scale and is typically reported using a summed score out of the maximum total summed score of 20. However, the raw scores are simply ordered points. The intervals between them are not equal, thus a total score of 16 may represent many different patterns of disability. In addition, because the scale is not linear, it is not possible to compare scores from two different scales, e.g. the BI and Functional Independence Measure (FIM), which measure the same construct because the relationship between the scales will vary according to the level of disability being measured.

More recently, scales have been assessed using two new psychometric methods: Rasch analysis and Item Response Theory, which overcome some of these difficulties. Both approaches model the probability of an individual's response to an item, in that a person with high levels of function will have an increased probability, relative to an individual with low levels of function of scoring more than zero on any item, e.g. whether rating dressing or toileting. These psychometric methods use statistical techniques that can be used to transform ordinal scales into interval scales. Thus, the relationship between one point and another both within and between items can be given a specific value. This has a number of potentially exciting consequences. First, it will provide a more accurate measurement of both individuals and groups, making it easier to assess the impact of treatment. The ability to measure change more accurately means that the numbers needed to detect significant differences between groups may be smaller. Secondly, it will be possible to compare groups measured using different scales, with enormous impact on our ability to interpret systematic reviews and perform meta-analyses. Thirdly, with sufficient items, knowledge of the relationships between scales makes it possible to use them for comprehensive assessment of individuals rather than measurement of a number of unrelated functions.

One of the difficulties in evaluating a rehabilitation service is that many markers of a quality service may not directly affect outcome. Given the difficulty in running efficient coordinated services, systems that allow the evaluation of the rehabilitation process are invaluable. Evaluating process is facilitated by the development of an Integrated Care Pathway (ICP). An ICP is a document that maps the interventions that should occur during a specific episode of patient care. Typically, the ICP allows evidence-based practice to be operationalized for a specific setting. The benefits of ICPs lie in specifying the best possible method of delivering care and in describing the patterns of variances. A variance sheet may be used to record either departures from the pathway as a procedural variance or the reasons for non-achievement of goals. Individual variances are neither good nor bad; they are simply a method of recording what happened to a specific patient and the reasons for it, thus allowing for individualized patient care. The patterns of variances across a group of patients will identify strengths and weaknesses in the processes around particular episodes of care and permit incorporation of new ideas and remediation of problems. When combined with measurement tools it is possible to identify which aspects of care impact positively or adversely on outcome.

Vocational rehabilitation

Ludwig Guttman, a pioneer in the management of spinal injuries in the 1940s, stated that a successful outcome in rehabilitation is the return of a patient to tax-paying status. This approach to vocational rehabilitation may be welcomed by the Exchequer, but it reflects assumptions that may be erroneous, both about the relative value that an individual places on return to work and about the fact that resumption of employment may only be achieved at the expense of a reduction in other valued aspects of life, such as social, sexual and leisure activities. A broader definition recognizes that adults need meaningful occupation, and covers voluntary activity as well as home-making and leisure activities. Although a popular view is that work is onerous and stressful, there is clear evidence that work leads to better quality of life, improved mood and greater life expectancy.

Nevertheless, until recently, proactive vocational rehabilitation has been neglected. At diagnosis, 98% of people with progressive neurological conditions such as MS are in work. Within 10 years most are unemployed. Thirty per cent of people with stroke are under 65 years of age. Most then retire and do not return to work. The rate of work return for people with spinal cord injury and paraplegia is 15% in the UK and 60% in Canada. In the UK, most people going on to benefit have relatively minor disability and expect at some time to return to work; only 0.7% of recipients of incapacity benefit have had a stroke, 0.2% have tetraplegia and 0.9% have MS.

The chances of returning to work after 1 year once on incapacity benefit are less than 20%. The reasons for this are complex but include the demands imposed by the job itself, the limitations imposed by the illness or disability and the barriers and expectations created by the society we live in. Vocational rehabilitation aims to overcome the barriers faced by an individual with an injury, illness or disability when retaining, returning to or starting work. It includes the support needed by both the individual and the employer and may involve:

1 Re-training, e.g. for a bricklayer who has become paraplegic.
2 Capacity building, e.g. increasing exercise tolerance in an individual who has become unfit as a result of fatigue.
3 Return to work management by employers, e.g. a graded return to work over a period of weeks or months following meningitis.
4 Reasonable adjustments at work – these include:
  - Changing recruitment and selection procedures;
  - Modifying work premises, e.g. making ramps, modifying toilets;
  - Changing job design, work schedules or other work practices, e.g. swapping duties among staff, permitting people to work from home or regular breaks for those with fatigue;
  - Modifying equipment, e.g. the provision of voice-activated software for those with upper limb problems or an amplifier-adapted telephone for the hearing impaired;
  - Providing training or other assistance, e.g. induction programmes for staff with a disability and co-workers who ensure staff with a disability can gain access to training.

5 Disability awareness – being aware of how society and individuals perceive people with disability, how this is reflected in the media, literature and the arts and how this influences behaviours.
6 Symptom management and rehabilitation, e.g. being aware of the roles of other professionals such as occupational therapists and physiotherapists in vocational rehabilitation.

Most adults who acquire disability through neurological disease use the hospital consultant or the general practioner as their first point of contact. Early and mild disability such as fatigue, or more effortful walking may impact on work before they impact on other areas of life. No matter how good an individual's clinical treatment may be, if they lose their job unnecessarily then treatment has, in part, failed them. Early intervention has two main advantages. The individual can identify the best way to disclose their illness and disability within the workplace. This is very different from disclosure to family and friends. Secondly, means of ameliorating the impact of disability can be identified, so work performance can be maintained and loss of goodwill within the workplace avoided. The individual's ability to access timely advice and support therefore depends upon clinicians, who should consider the following steps:

- Ask about work, the impact of work on the disease and the disease upon work.
- Discuss disclosure.
- Identify if the individual has access to an occupational health department. One of the major roles of the occupational health physician is assessment of disability and fitness to work. As few as 30% of the UK population have access to a specialist occupational health service.
- In the UK, make individuals aware of the role of Disability Employment Advisors (DEAs) and the Access to Work scheme. DEAs provide specialist support for those wishing to move into employment or retain an existing job in the event of disability and are based in JobCentrePlus. The Access to Work scheme provides funding for costs that an employer may incur because of an employee's disability, and most commonly is used to provide support with transport costs to work for individuals who cannot use public transport or drive. Other support can be provided such as a powered wheelchair for use at work, adapted desks, specialist software or adaptations to premises.
- Refer the patient to occupational therapy services.
- Remind and inform the patient of the terms of the Disability Discrimination Act. It is unlawful to treat disabled people less favourably than others for a reason related to their disability. Employers have to make reasonable adjustments for disabled people, including modifying physical barriers to access. Schools, colleges, universities and providers of adult education and youth services also have to ensure that they do not discriminate against disabled people.

Single incident brain injury

Stroke and head injury are two of the most prevalent neurological conditions affecting the CNS. They involve very different populations, with contrasting clinical needs and expectations, which highlight important questions relating to neural protection and restoration, service delivery and routes to improving participation and life quality. In white populations about 90% of stroke patients are over 65 years of age compared with some 20% of patients following head injury. Both conditions result in an annual incidence of hospital admission of 1–3/1000 adults. Following head injury only 10–20% of patients remain in hospital for more than 3 days, because 80–90% of injuries are mild, while after stroke such brief admission is now the exception. The prevalence of substantial disablement after stroke is 5–8/1000 population and after head injury at least 1/1000. This latter figure may be greater if the incidence of newly disabled adult survivors after TBI is 100–150/100,000, because the younger age groups over-represented in this population usually have a near-normal life expectancy of 30–40 years even after severe injury.

In the UK, stroke is the most common single cause of severe physical disablement in people living at home. Six to twelve months post-stroke only 60% of patients presenting with hemiplegic stroke have achieved independence in personal care. Of survivors, 30–40% are depressed, 10–15% severely so. Fifty per cent need help with either housework, meal preparation or shopping. A similar number lack a meaningful social, recreational or occupational activity during the day. Not only are the personal costs of stroke enormous, but also the economic consequences. In the UK the annual costs of direct and informal care and lost productivity was estimated by the National Audit Office in 2005 at £7.0 billion; these costs will increase as the population ages. Similar data describing the overall economic burden of head injury in the UK are not available but must be of at least similar magnitude assuming the prevalence outlined above; costs are estimated at about $50 billion annually in the USA. This results largely from cognitive, affective and behavioural rather than physical impairments in a younger population, and thus impacts on less easily identifiable budgets than stroke over a longer period. A number of studies over the last 20 years have shown how over time post-injury mobility and independence in personal care are least affected while the ability to fulfil social roles remains problematic.

During the first few weeks after a significant single incident brain injury of any cause, acute in-patient rehabilitation should focus on the prevention of systemic and neurological complications (Table 17.6) while resolution of cerebral oedema, toxic-metabolic dysfunction and intracranial mass effects take place and should provide a basis for ongoing neuroprotection in parallel rather than in series with the initiation of restorative strategies (Figure 17.1).

During the next several months, early rehabilitation programmes focus on skill learning to reduce dependency in personal care and domestic and community-based ADL, while late programmes particularly address social roles and issues of life quality. The time post-injury when the components of these programmes (Fig. 17.3) should begin and end varies with a number of factors, particularly injury severity. Many of these issues are addressed in evidence and expert opinion based guidelines, produced in relation to stroke in the UK by the Royal College of Physicians (2004) and the Scottish Intercollegiate Guidelines Network (SIGN, 2004), in Australia by the National Stroke Foundation (2003) and in the USA by the American Stroke Association, the Department of Veterans Affairs and Department of Defense (2003). All are accessible via www.strokecenter.org/prof/guidelines.htm. Guidelines in relation to head injury and other acquired single incident brain injuries in the UK are those produced by the Royal College of Physicians and British Society of Rehabilitation Medicine (2003) and the Department of Health's National Service Framework (NSF) for Long-term Conditions (2005). Evidence, summarized below, for the effectiveness of components of these systems is largely derived from trials after stroke. Its application to rehabilitation after head injury is tempting but unproven.

Guidelines for hyperacute management and intensive and neurosurgical care after head injury are well established (e.g. National Institute for Health and Clinical Excellence, 2003). High dependency care, apart from that required for thrombolysis, is now being investigated acutely after stroke, to assess the benefits of providing continuous rather than manual monitoring for hypoxia, hyperglycemia, hypotension, cardiac arrhythmias and elevated body temperature during the first 48–72 hours after admission. This may result in improved outcome at discharge in more dependent patients and may reduce mortality at 3 months and 1 year in patients with severe stroke without increasing dependency.

Organized acute and early rehabilitation has been investigated in depth after stroke. A meta-analysis of 23 trials compared care in a stroke unit (SU), nine of which were comprehensive and included both acute (but not high dependency) and rehabilitation components with alternative services, usually in a general medical or geriatric ward with or without a visiting stroke team. Analysis showed that patients who receive unit-based in-patient care do not stay longer in hospital and are more likely to be alive, independent and living at home 1 year after the stroke, regardless of gender, age and stroke severity (Fig. 17.4). Results from nine post-acute units which admitted patients more than 1 week post-stroke, compared with an alternative service revealed similar benefits. Compliance with post-acute but not acute SU guidelines (Table 17.7) has been shown to correlate with outcome. The reduction in SU deaths probably results from fewer complications of immobility rather than neurological or cardiovascular complications. The increased number of patients discharged home, rather than to institutional care from SUs is largely attributable to an increase in the number of patients returning home physically independent (Rankin score 0–2), rather than dependent (Rankin score 3–5) This is described in the Stroke Unit Trialists' Collaboration (1997).

Aspects of care common to acute and rehabilitation SUs include:

- Comprehensive medical, nursing and therapy assessments;
- Integration of nursing care within the multi-disciplinary team;
- Early mobilization and treatment of hypoxia, hyperglycaemia, suspected infection and avoidance of urinary catheterization;
- Formalized goal-orientated multi-disciplinary team care, with early discharge planning and education and involvement of carers.

Many of these aspects of care are not delivered by a peripatetic specialist stroke team (PSST). In one study, complications including stroke progression, chest infections and dehydration were less frequent in the SU. More patients were dead or institutionalized (30% vs 14%; $P < 0.001$) and fewer were alive without severe disability (66% vs 85%; $P < 0.001$) in the group allocated to the PSST.

Table 17.6 Avoidable generic and specific complications after brain injury and their management.

Cause and effect	Management
Co-morbidities	
Hyper-/hypo-tension	Antihypertensives/treat cause
Cardiac events	Specific medical treatments
Fever	Antipyretics
Gastrointestinal bleeding	? Prophylaxis; avoid NSAIDs
Drug side-effects	Drug withdrawal
Musculoskeletal pain	Physical therapies
Polytrauma	Refer to other specialties
Physical dependency +/– neural injury	
Pressure sores and skin breaks	Pressure care, and 24-hour handling
Contractures and shoulder pain	& positioning
PEs and DVTs	Thromboprophylaxis
Falls	Risk assessment
Constipation and faecal impaction	Bowel regime and toiletting programme
Aspiration and chest infections	Tracheostomy and dysphagia management
Urinary tract infections	Toiletting programme, +/– drugs
Malnutrition and dehydration	Dysphagia management and dietetics
Detraining	Aerobic exercise programmes
Brain injury	
Hydrocephalous, mass effects and rebleeds	Neurosurgical management
Confusion and agitation	Environmental management +/– drugs
Autonomic storms	Time and drugs
Epilepsy	AEDs if no other trigger
Sleep-disordered breathing	CPAP ventilation
Spasticity	Spasticity management
Vegetative and minimally aware states	Avoid misdiagnosis
Emotionalism	Time and antidepressants
Heterotopic ossification	Etidronate +/– NSAIDs
Late maladaptive behaviours	Behaviour modification programmes
Involuntary movements	Drugs and DBS
Central pain	Pain management techniques
Fatigue	?Retraining
Catastrophic illness	
Critical illness neuromyopathy	Multidisciplinary retraining
PTSD, depression and anxiety	CBT +/– drugs
Family breakdown	Information + training

AEDs, antiepileptic drugs; CBT, cognitive behaviour therapy; CPAP, continuous positive airway pressure; DBS, deep brain stimulation; DVT, deep vein thrombosis; NSAID, non-steroidal anti-inflammatory drug; PE, pulmonary embolism.

Remarkably, the differences between SU and alternative care persist for many years. Even 10 years after randomization to an acute and rehabilitation SU or a general ward, fewer SU patients had died (75.5% vs. 87.3%; $P = 0.008$), more were at home (19.1% vs. 8.2%; $P = 0.018$). More were at least partly independent with a BI score of ≥60 (20.0% vs. 8.2%; $P = 0.012$), if not independent with a BI score of ≥95 (12.7% vs. 5.4%; $P = 0.061$). Increased survival times have been observed 5 years after randomization to a SU versus a general medical or geriatric ward.

Early discharge of medically stable patients with support by a multi-disciplinary outreach team after mild and moderate stroke, with an admission BI of >9/20, adds to initial SU gains. A meta-analysis of individual patient data from 11 trials of early supported discharge (ESD) versus conventional care in patients moderately disabled at discharge (median discharge BI 15/20) showed:

- A reduced risk of death or dependency (0.79 [0.64–0.97]; $P = 0.02$) in the ESD group

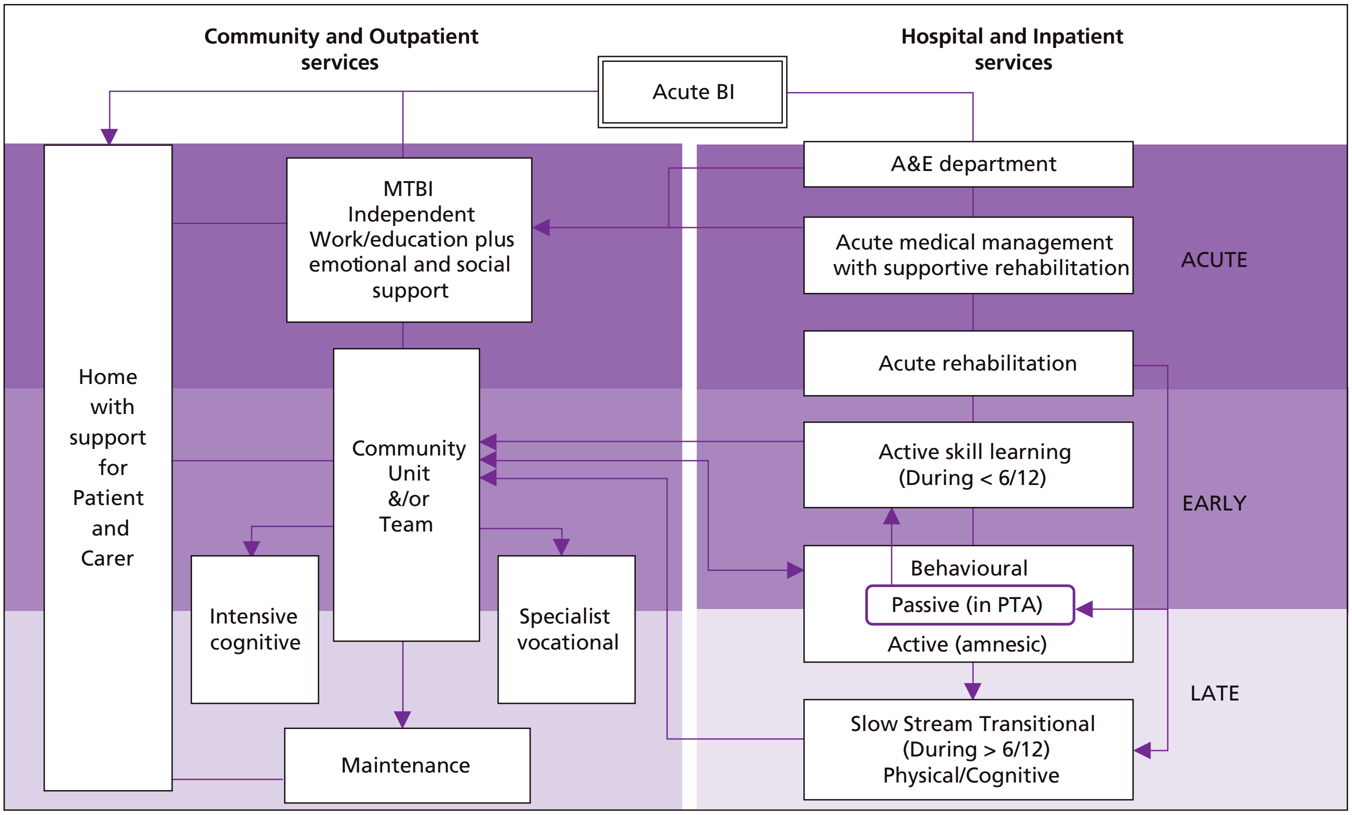
Community and Outpatient services
Hospital and Inpatient services
Acute BI
A&E department
Acute medical management with supportive rehabilitation
ACUTE
MTBI Independent Work/education plus emotional and social support
Acute rehabilitation
Home with support for Patient and Carer
Community Unit &/or Team
Active skill learning (During < 6/12)
EARLY
Behavioural
Passive (in PTA)
Active (amnesic)
Intensive cognitive
Specialist vocational
LATE
Slow Stream Transitional (During > 6/12) Physical/Cognitive
Maintenance

Figure 17.3 Classification of rehabilitation services after single incident brain injury (BI) by time, severity and need. Acute medical and surgical management varies by pathology and is described elsewhere. The rehabilitation options illustrated can be defined and coded to clarify gaps in service provision and clinical pathways. MTBI, mild traumatic brain injury. (After Pickard *et al*. 2004).

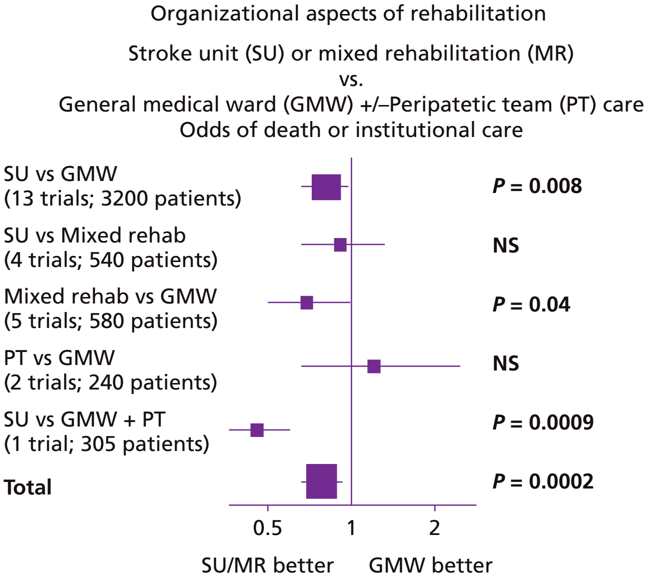

Figure 17.4 Care in stroke or mixed rehabilitation units can be organized and is thus more effective than in general medical wards with or without input from a peripatetic team, where it remains disorganized. (Stroke Unit Trialists' Collaboration, 2001.)

Table 17.7 Compliance with these dimensions of process during post-acute rehabilitation after stroke correlates with outcome. (After Duncan P, Horner R, Reker D, *et al*. Adherence to post-acute rehabilitation. Stroke 2002; **33**: 167–178.)

1 Multidisciplinary team coordination
2 Baseline assessment
3 Goal setting
4 Treatment plan
5 Monitoring of progress
6 Management of impairments/disabilities
7 Prevention of complications
8 Prevention of recurrent stroke
9 Family involvement
10 Patient and family education
11 Discharge planning

- Hospital stay shortened by 8 days ($P < 0.0001$)
- Significant improvement in extended ADL ($P = 0.05$), although not in subjective health status or mood in either patients or carers.

Two more recent studies found that these gains can include better life quality, assessed by the Nottingham Health Profile, at 1 year and that gains in domestic and extended ADL are still evident after 5 years.

Once in the community, patients are known to be at risk of deteriorating after stroke as a result of multiple health problems including falls, depression, physical and social inactivity and isolation, in addition to age-related symptoms and co-morbidities. Health-related quality of life declines in the 6 months after discharge. The place for, and optimal process in, residential service systems other than SUs for patients later after stroke remains to be examined. A meta-analysis of trials of therapy-based outpatient or domiciliary rehabilitation, delivered by either a multidisciplinary team or by a physiotherapist or occupational therapist, with the goal of improving task-orientated behaviours, has shown that deterioration is prevented (OR 0.72 [95% CI 0.57–0.92]; $P = 0.009$) and dependency in personal care reduced (95% CI 0.02–0.25; $P = 0.02$). The effective components and best location for this type of service need further exploration, but benefit has been consistent in trials of community-based occupational therapy. A meta-analysis of eight trials showed that intervention was associated with improved personal, extended and leisure-based ADL depending on the intervention target. These findings are confirmed in more wide-ranging systematic reviews of occupational therapy for stroke patients. Most studies of physiotherapy in patients in the community after stroke investigate the effect of a particular physiotherapy treatment on improving upper or lower limb function at the level of impairment and mobility, which may improve, rather than limitations in activity and independence, which if examined may not. Domiciliary physiotherapy within 6 months post-stroke has been shown to reduce risk of re-admission after an average of only 2.9 (range 1–8) visits and reduces dependency at less cost compared with day hospital attendance. In patients more than 1 year post-stroke as few as 4–5 physiotherapy sessions produced a clinically small but significant improvement in mobility.

Informal carers should be recognized as an important resource. They enable patients to remain in the community and their support is likely to facilitate patient outcomes. The levels of depression in the patient are greater in those who feel poorly supported. Formal support for carers, rather than assistance for patients, is often more difficult to obtain. Trials of psychosocial interventions to support stroke carers using information packages, specialist nurses, a mental health worker or family support workers have failed to show functional or psychological benefit in patients and only modest psychosocial benefit for carers. By contrast, there is evidence to suggest that carer adjustment is increased by education and counselling or by training in social problem-solving skills. Training informal carers in basic nursing skills and facilitation of personal care techniques reduces costs and caregiver burden; this improves psychosocial outcomes for both carer and patient, although there is no change in patient mortality, institutionalization and disability.

It seems likely, although unproven, that many of the lessons learned from trials of acute, early and later rehabilitation after stroke are applicable to similar components of rehabilitation required after diffuse brain injury, most frequently traumatic (Figure 17.3). The evidence base derived from group studies for TBI is meagre by comparison. This reflects both the relatively small numbers of patients requiring in-patient care for more than a few days after head injury and the difficulties involved in community follow-up of the larger number of patients with less severe injuries, many of whom are disadvantaged and peripatetic pre-injury and cognitively impaired post-injury.

For those patients requiring protracted in-patient stays after severe TBI, historical evidence emphasizes the importance of preventing the physical complications of immobility, just as it does after spinal injury. Studies in the late 1960s from the USA documented frequent pressure sores, joint contractures and frozen shoulders in patients late after severe head injury, problems that are now less frequently seen. Since that time, many studies from North America, facing a prospective payment system for rehabilitation, have investigated, often retrospectively, measures of dependency that reliably predict resource use but have not compared different rehabilitation systems prospectively. In the UK and mainland Europe the tendency has been to resort to dialogue and protest with funding authorities via consensus and expert opinion.

There are only two studies, both retrospective, that attempt to investigate the effect of integrating rehabilitation into acute care following admission and intensive care after moderate or severe head injury. The first is that of Mackay *et al.* (1992) who retrospectively compared outcome on discharge from an Early Rehabilitation Unit (ERU) in 17 patients who had received aggressive rehabilitation during acute hospitalization in one hospital for 51.5±6.8 days, with 21 control patients matched for injury severity and acutely hospitalized without focused acute rehabilitation (AR) in 10 different hospitals for 64.1±7.8 days before both groups were transferred to the same ERU. Length of stay in total and in early rehabilitation was halved in the group receiving AR, 94% of whom returned home at discharge versus 57% in the control group. However, in the absence of good reason to think that AR could reduce coma duration, one has to assume that the results were confounded by a coma duration of 19 days in the group that received AR versus 54 days in the control group ($P = 0.03$). A more recent study at the National Hospital of AR after head injury retrospectively compared resource use in 92 patients receiving unit-based AR with a parallel group of 97 patients undergoing usual care. About 10% of patients admitted via accident and emergency departments required AR after neurosurgical consultation or care, after which mean length of stay in AR was about 3 weeks and was not prolonged compared with usual care. In addition, referral to community-based rehabilitation services was significantly increased in patients discharged from AR compared with those discharged from neurosurgical care.

Other group studies of in-patient rehabilitation after head injury address the benefits of early active participation inpatient rehabilitation, which in the UK starts a month or more after injury, rather than AR in parallel with and immediately after neurosurgical treatment. Most, from North America or the UK, are non-randomized retrospective or prospective comparisons of two groups. They still emphasize the economies in resource use resulting from reduced lengths of stay in rehabilitation as well as acute care, with at least equivalent (if not improved) functional outcomes that are said to result from early transfer to rehabilitation. One two-centre study investigated outcome after moderate and severe injury in 24 patients who were randomized prospectively to receive supplemented in-patient rehabilitation versus 27 patients who received the usual programme. The supplemented group made greater gains in functional independence by the time of discharge during a similar length of stay.

Prospective randomization of the far greater number of less severely injured patients early after injury presents fewer methodological problems because there are more patients and cheaper treatment options. These patients have usually mobilized and moved into the community but experience many cognitive, affective, behavioural and somatic post-concussional symptoms. However, compliance with follow-up and treatments is difficult to ascertain unless trial entry is limited to patients who are not premorbidly disadvantaged, e.g. athletes or military personnel. One trial prospectively randomized military personnel, who had recovered independent mobility and returned home with supervision within 3 months of moderate and severe head injury, to either 8 weeks of an in-patient cognitive–behavioural community and vocational re-entry programme costing \$51,840 ($n = 67$) or a low cost (\$504) cognitive and exercise-based home programme with weekly telephone support from a psychiatric nurse ($n = 53$). Both treatments were followed by a 6-month graded return to limited military duties. Some 40% of patients recruited to the study had a PTA of 7 days or more and some 35% had been unconscious for 24 hours or more. At 1 year post-treatment, overall there was no difference in the two groups in return to work or quality of life measures, but of patients unconscious for more than 1 hour initially ($n = 75$), 80% were fit for duty in the hospital group versus 58% in the home-based group ($P = 0.05$). There was a trend ($P = 0.13$) in favour of the home-based group in patients ($n = 44$) unconscious for an hour or less.

Other prospective randomized group studies early after injury have recruited less severely injured patients and investigated the effect on post-concussional symptoms of psychological interventions including reassurance, information giving and advice. These have found that intervention is associated with significant reduction in the intensity and number of symptoms and quicker return to work. One study investigated outcome at 6 months in patients admitted to hospital after head injury. Cases were randomized to usual care or a programme of face-to-face interviews with written advice about likely prognosis and recovery times and the management of post-concussional symptoms. These included reduced speed of information processing, memory problems, the interaction of cognitive and emotional stress, post-concussion symptoms, post-traumatic stress and a graduated return to normal levels of activity. This found that in patients with a PTA between 1 hour and 7 days, intervention was associated with significant reduction of concentration difficulties, headaches, fatigue, sleep disturbance and irritability with improvement in the patient's relationship with a partner, ability to cope with family demands, participate in social activities and enjoyment of leisure activities. Only 12% had more than one face-to-face contact. The economic benefits of this relatively low cost intervention in these patients, 70% of whom still had post-concussional symptoms and/or psychosocial problems at 6 months post-injury has not been investigated.

Late after moderate and severe injury, gains in community and vocational function and life quality are usually limited by residual cognitive, affective and behavioural problems, rather than physical difficulties. However, adaptive change may continue for years, especially in younger patients and with the judicious prescription of goal-focused interventions and ongoing support, which may need to be life-long. One UK study prospectively randomized 110 patients a median of 1.37 years after largely severe injury to either a multi-disciplinary outreach programme twice a week for a mean of 27 weeks or to written advice. Two years after recruitment there were still significant gains in outreach treated patients in measures of community independence and self-organization but not in socializing, productive employment or mood. After severe injury, the high rate of unemployment in this young population of 50–70% compared with rates of 10–20% pre-injury is now well documented. Work retraining and supported employment models have been described over the last 20 years. Their efficacy, sometimes achieving employment rates of above 50% late after severe injury, has so far been gauged against a pre-intervention baseline rather than a prospectively randomized control and tends to assume rather than demonstrate improved life quality with employment. Nevertheless, specialist programmes of this sort are important aspects of the rehabilitation menu in clinical practice.

Disorders of personality and behaviour after exit from PTA, usually involving irritability, impulsivity and verbal aggression often triggered by minor increases in environmental demand, which are containable by informed family and non-specialist support in the community are relatively common after severe head and other non-focal brain injuries. They may deteriorate with time, particularly in the absence of rehabilitation provision. These problems are more difficult for carers to tolerate and manage than long-term physical and cognitive deficits and are well-recognized causes of marital breakdown, social isolation and recurrent unemployment. Management is advocated with programmes of various intensities on an out-patient or day-patient basis to deliver cognitive rehabilitation, cognitive–behaioural therapy and psychotherapeutic strategies, sometimes with adjunctive drug treatment such as carbamazepine or an antidepressant. In the longer term this promotes insight and a structure within which it is possible to plan and set realistic goals and thus reduce anxiety and maladaptive behaviours. Aggressive or sexual behaviours sufficiently aberrant to require residential modification are uncommon although resource demanding, particularly when accompanied by psychiatric disorders, which can be preexisting. They require the application of behavioural frameworks that modify and reduce aggressive behaviour even years post-injury. Improvement in life quality resulting from these complex cognitive and behavioural interventions has so far proved difficult to demonstrate.

In addition, the long-term sudden change in independence and social roles that occurs as a result of severe brain injury requires disability management life-long if optimal function is to be maintained and deterioration prevented. Complications such as falls and further injuries, depression and social isolation, fits or substance abuse are largely avoidable. Provision for those patients who are mobile in the community should include low cost specialist day centres, such as Headway Houses in the UK and also access to a professional, often a clinical neuropsychologist with experience of the consequences of acquired brain injury for support and to facilitate change over extended periods of time. Recent reports of patients in low awareness states regaining reliable awareness after very long periods, with or without neural stimulation or drugs, suggests that late and slow, albeit functionally relatively minor improvement in more dependent patients requiring long-term residential placement may also occur over many years, given good care, and begs the question as to whether the changes seen are the result of structural plasticity.

Postscript

Not too long ago, many neurologists equated rehabilitation and therapies with water divining and the darker arts. Over the last 20 years there has been a *volte face* amongst clinicians, driven by studies over the last 50 years in the basic neurosciences and confirmed more recently by work in primates and the results of multi-modal functional imaging of neural reorganization in the damaged human brain. This work has eloquently confirmed Donaldson's statement in 1895 that 'in the central nervous system . . . the cell elements are . . . plastic in the sense that their connections are not rigidly fixed, and they remember . . . By virtue of these powers, the cells can adjust themselves to new surroundings.' Cajal's subsequent statement to the contrary in 1928 that '. . . the nerve paths are something fixed, and immutable' was, according to Finger and Stein in 1982, swept aside by the emerging restorative neurosciences: 'Until very recently, prevailing concepts of brain function precluded the possibility of structural and neurochemical reorganization of function; theoretically, once damage occurred, the possibility for rehabilitation was to train the patient to use alternative, but less effective, behavioral strategies.'

There is an undercurrent to this statement which implies that the new science has a route to normalization and a means of reversing the natural order, an agenda beloved of basic science and indeed its audience. But clinical experience still emphasizes that:

- Neural injury generally results in an irreversible step-change at least in structural and physiological if not observable functional status; and that
- Following injury, the most obvious functional gains result from the prevention of complications, whether physical, cognitive, behavioural or emotional, and from adaptive interventions that include environmental modification, rather than neural restoration.

However, if complications are prevented, and use is allowed or even forced, then neural reorganization generated by daily activities follows. Acknowledgement of injury, and consequently loss, if only by the healer, is first required before it becomes possible to admit the importance of complications and their prevention, and allow neural reorganization, before going on to investigate and use (new) techniques that drive neural reorganization. Both approaches necessarily use remaining neural structures and networks but, at least for the foreseeable future, still result in 'alternative, but (inevitably) less effective, behavioural strategies'.

The widespread adequate longitudinal provision of strategies that prevent complications and allow, and possibly drive, neural reorganization have not been achieved even by health services in industrialized economies. To do so requires major reorganization of funding as well as healer behaviour, so that goal-focused retraining programmes using individualized current best practice can be routinely provided, life-long if needed. A regime change of this sort would probably result in further significant reduction in morbidity and mortality in the long term after neural injury, and should be facilitated by an increase in the translation of ideas from the basic (social) science of organizational behaviour into clinical multi-disciplinary team working.

This clinical process is separate from but complementary to the exploration of novel restorative treatments, studied in cohorts-triaged by robust subject and disease-related variables and using MRC methodology to trial complex interventions, that:

1 **Allow** neural reorganization by preventing complications, resulting for example by:
  - Spasticity, using new drug targets or stimulation techniques;
  - The detraining and soft tissue effects of immobility, using novel in-patient and community-based retraining programmes; and
  - The impact of cognitive and emotional dysfunction on attention and thus learning and compliance with training programmes, using drugs and cognitive rehabilitation and conditioning techniques.

2 **Drive** neuroplastic changes by:
  - Repetitive goal-directed skill learning, motor imagery or action observation;
  - Interventions that condition neural structures using different neural stimulation techniques and/or drugs; and

- Neural regrowth and replacement techniques that appear to achieve dramatic effects in animal studies but have as yet to be trialled in humans.

Treatments that combine these principles, and for example simultaneously prevent complications and drive neural reorganization or use intensive training to drive the induction of structural plasticity in useful directions, are likely to produce most functional gain. Such a conjunction fortuitously occurs in CIMT, which uses both constraint to induce or force use of an underused motor system and movement therapy, as massed practice, to drive motor output and shape use. CIMT has recently been shown to be functionally effective in a ground-breaking Phase III trial in the USA, albeit at a cost of $7.5 million over 5 years. Delivery of conventional CIMT is limited not only by functional entry criteria, which require some wrist and finger movement, but also an intensive schedule comprising constraint of the less affected hand for most of 14 consective days and one-to-one training of the affected hand for 6 hours a day for 10 of those days. While this would not preclude its use for short periods to drive inducers of structural plasticity, at present, at least in the UK, CIMT remains a poor candidate treatment to carry over into routine clinical practice. This is because of problems both with therapy resources and patient compliance, although modified CIMT for shorter sessions over longer periods may prove equally effective. Similar delivery problems apply to many other physical therapies and stimulation techniques, for which questions of therapy intensity and length also arise.

Conditioning stimulation techniques and/or drug therapies might reduce training requirements, and thus facilitate not only the introduction of therapies into clinical practice but also their use in the longer term. Invasive stimulation techniques are likely to have at best limited application; the effectiveness and robustness of different types of non-invasive magnetic and electrical stimulation of the brain and peripheries, alone and in conjunction with standardized therapies, needs comparison. Similar investigation is needed of different drugs that modulate neural excitability and regrowth and promote skill learning, both those that are already available and novel preparations.

Chosen therapies and conditioning techniques need first to be standardized and then investigated in proof-of-concept and Phase II studies before Phase III trials can be achieved. This framework underpins a huge variety of studies, using both physiological and functional entry and outcome measures, to define which treatment or treatments work, how to use them, when to use them following neural injury and for what type and level of impairment. Patient recruitment to studies of therapy or stimulation interventions is difficult, e.g. a rate of one patient per month per site being achieved in the recent CIMT trial, but is likely to be easier in drug studies. Just as functional imaging's major, if inadvertent, contribution to clinical practice has been to change attitudes to the prescription as well as the practice of rehabilitation, so the demonstration in small studies in the laboratory that restorative treatments can result in useful functional change is likely to encourage the addition of an exploratory element to many patients' coping strategies and increase recruitment to Phase III trials intended to translate these treatments into the clinical domain.

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18

Toxic, Metabolic and Physical Insults to the Nervous System and Inborn Errors of Metabolism

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Toxic, nutritional and metabolic derangements can cause damage to the nervous system by a variety of mechanisms leading to a wide spectrum of characteristic neurological disorders. Exposure to toxic substances, which may be accidental or deliberate in the context of substance abuse, can cause encephalopathy, stroke, seizures or neuropathy. Nutritional deficiencies are probably the most common worldwide cause of neurological disease and are manifest as a number of well-characterized, usually reversible but potentially serious neurological disorders. Metabolic encephalopathy is brought about by the consequences of organ failure or exposure to endogenous or exogenous toxins or drugs which may affect the central or peripheral nervous systems. The cause of these conditions may be unclear at presentation and often requires detailed clinical and laboratory analysis before the correct diagnosis can be made and appropriate therapy instituted.

Neurological disorders associated with exposure to toxic substances

Environmental factors and toxins are important causes of neurological disease. They are often under-recognized and are difficult to diagnose as the onset of symptoms may be slow and the clinical pattern may mimic other common conditions. This chapter includes a review of the effects of accidental and deliberate exposure to industrial and environmental toxins and drugs of addiction including alcohol. Some of the more important toxins that affect the nervous system are shown in Table 18.1.

Heavy metals

Exposure to heavy metals or industrial toxins is usually cumulative, developing over a prolonged period of months or years as a consequence of environmental or occupational exposure. However, these agents may be acutely toxic with accidental or deliberate ingestion of excessive amounts. The adverse effects of acute or chronic exposure develop earlier and more rapidly in the young and the consequences differ from those in adults. Heavy metals impair the function of the nuclei or cytoplasmic structures, particularly mitochondria. Acute exposure often leads to encephalopathy with confusion, attention deficit and seizures, while chronic involvement is of a more insidious onset with mood disturbance, memory and cognitive impairment. Systemic features usually accompany neurological manifestations.

Lead

Lead is the most common source of heavy metal intoxication because of its extensive commercial use and presence in Ayurvedic medication. Occupational exposure occurs in workers in smelting and metal foundries, battery manufacture and industrial plants. Accidental ingestion occurs in children with *pica* (eating dirt); however, exposure has diminished with the phasing out of leaded petrol and diminished use of lead-based paints. Inorganic lead is absorbed from the gastrointestinal tract and children are particularly vulnerable. Lead binds to erythrocytes and is distributed throughout the body; it is incorporated into the brain and other soft tissues where it may persist for prolonged periods. It is toxic to the nervous system and leads to altered migration of neurones during development; it also interferes with cell membranes, neural cell molecules, myelin, neurotransmitter function and calcium metabolism.

Lead toxicity has a number of effects in the nervous system leading to acute encephalopathy (particularly in children) and polyneuropathy in adults. Lead encephalopathy may follow gastrointestinal symptoms and patients present with headache and fatigue leading to confusion, altered level of consciousness, behavioural change and focal or generalized seizures. They may develop ataxia, impaired motor function or lapse into coma. In children, lead is a significant neurodevelopmental toxin, which produces mild learning difficulties. In adults, chronic exposure leads to a similar but slower onset encephalopathy characterized by headache, myalgia, paraesthesia, irritability, sleep disturbance and loss of libido evolving into progressive confusion and stupor.

Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

Table 18.1 Toxins that affect the nervous system.

Metals
Lead
Mercury
Arsenic
Manganese
Aluminium
Thallium
Tin
Bismuth

Solvents and small molecule toxins
Ethanol
Methanol
Toluene
Trichloroethylene (TCE)
Tetrachlorethylene (perchlorethylene, PCE)
Ethylene oxide
Hexacarbon solvents include n-hexane and methyl n-butyl ketone (MnBK)
Xylene and styrene
Carbon disulphide
Cyanide
Acrylamide
Allyl chloride
Methyl bromide
Methyl chloride
Nitrous oxide
Organophosphates
Carbon monoxide

Natural toxins
Plant toxins
Fungal toxins
Marine toxins
Insects and animals
Snake bites
Spider
Scorpion
Botulinum toxin

Pure motor neuropathy may occur affecting the upper more than the lower limbs. The onset is usually symmetrical and often associated with prominent gastrointestinal disturbance. There may be bilateral wrist or foot drop with marked atrophy and occasional fasciculation, which may mimic motor neurone disease. Although the sensory component is usually minor, the neuropathy may be particularly painful. Lead toxicity can cause a blue line at the gingival margin.

Investigations will show elevated levels of lead, there is a hypochromic microcytic anaemia with basophilic stippling of the red cells, hyperuricaemia, reduced blood δ-amino-laevulinic acid and raised zinc and lead protoporphyrins. Nerve conduction studies show a marked axonal neuropathy with denervation although there may be mild motor conduction slowing. Nerve biopsy confirms axonal degeneration although paranodal demyelination may be present.

The mortality of acute severe lead encephalopathy may be >25%. Treatment is initially supportive and involves eliminating the continuing source. Chelation therapy is used to remove lead before it can be incorporated into the CNS or soft tissues. This involves treatment with EDTA, dimercaprol (2,3-dimercaptopropanol) or D-penicillamine. Early treatment usually leads to improvement in the neuropathy but the prognosis of the encephalopathy is less certain.

Mercury

Mercury exists in an elemental inorganic or organic form. The inorganic form is absorbed rapidly following inhalation during industrial exposure in the production of thermometers, barometers or batteries and traditionally was also ingested during hatmaking. The organic form, methyl mercury, is far more toxic and occasionally poisons water supplies, notably in the Minimata outbreak in Japan. Methylmercury is bio-amplified by aquatic species and causes paraesthesiae, tremor, ataxia, spasticity, progressive visual field and hearing loss with encephalopathy, progressing to stupor, coma and death. Chronic industrial exposure to elemental or inorganic mercury causes systemic manifestations with renal, skin, pulmonary and gastrointestinal involvement including cutaneous erythema, anaemia and proteinuria. Patients develop progressive rest and intention tremor ('hatter's shakes'), ataxia and myopathy; there is memory and cognitive impairment, social withdrawal, personality change with anxiety, excitability, emotional lability and insomnia. Eventually, drowsiness, confusion and stupor supervene. Diagnosis is confirmed by demonstrating elevated blood and urine mercury. Treatment is by facilitating the elimination of mercury with prompt chelation using penicillamine and providing supportive care. The role of chelation therapy with dimercaprol is controversial.

Arsenic

Arsenic has been used as a poison because it is odourless, tasteless and highly toxic. It has been extensively employed in herbicides and pesticides and as a timber preserver in the past, although current use is mainly restricted to the production of glass, electronics and computer microchips. Exposure occurs by drinking contaminated well water, especially in the Indian subcontinent, or as a consequence of mining lead or copper smelting; arsenic is sometimes found in herbal medications. The mode of action is to inhibit mitochondrial function and oxidative metabolism. Acute or subacute exposure is associated with nausea, vomiting, abdominal pain and bloody diarrhoea, followed by progressive encephalopathy. Autonomic features including hypotension, tachycardia and vasomotor collapse develop culminating in arrhythmia, myoglobinuria, acute renal failure, obtundation, acute confusional state, coma and death. Low dose chronic exposure causes weight loss, severe alopecia and white horizontal striations on the nails (Mees' lines). There is usually severe gastrointestinal disturbance and skin changes include melanosis, keratosis and malignancy. There may be personality disturbances with confusion, irritability, delusions and visual hallucinations; optic nerve and spinal cord involvement can also occur. Arsenic neuropathy is predominantly axonal although demyelinating features occur soon after exposure. It usually develops within several weeks of the acute exposure and is characterized by distal pain and progressive weakness initially in the lower limbs, subsequently spreading to the upper limbs with areflexia and distal sensory loss. The neuropathy is associated with respiratory muscle weakness. Investigations may show myoglobinuria, elevated liver enzymes and CSF protein. Arsenic binds to keratin and therefore can be detected in hair, nail or urine. Nerve conduction studies show motor and sensory axonal neuropathy with occasional demyelinating features and nerve biopsy confirms axonal degeneration. Treatment involves removal of exposure, decontamination of the gastrointestinal tract and aggressive support. Chelation therapy may be undertaken with derivatives of dimercaprol such as 2,3-dimercapto-1-propanesulfonic acid (Unithiol) or D-penicillamine but there is little evidence to suggest this helps in the later stages of arsenic neuropathy.

Manganese

Manganese is present in all living organisms and functions as an enzyme cofactor. It is widely used as a fuel additive and also in fertilizers and fireworks. Toxicity occurs as a consequence of its industrial use in iron and steel manufacturing and in welding but exposure may also be iatrogenic as a consequence of poorly balanced total parenteral nutrition. Acute exposure may lead to a progressive encephalopathy (‘manganese madness’) characterized by fatigue, apathy, insomnia, auditory and visual hallucinations, personality change, compulsive behaviour, irritability and aggression culminating in progressive memory disturbance. More chronic exposure leads to a characteristic pattern of extrapyramidal abnormalities characterized by parkinsonian facies, hypersalivation, micrographia, bradykinesis, rigidity and severe dystonia with occasional myoclonic jerking. There is often an associated encephalopathic component including emotional lability and progressive cognitive impairment. The diagnosis is confirmed by the presence of elevated serum manganese and urine levels may also be helpful. MRI scan may show abnormal signal intensities in the globus pallidus and subthalamic nucleus. Management necessitates removal of the toxic sources and chelation with EDTA is occasionally helpful. The response to levodopa is variable. Dialysis may be necessary.

Aluminium

Aluminium is abundant and is extensively used in packaging, food containers and cooking utensils and in water treatment. Industrial exposure may occasionally occur after smelting or inhalation of aluminium dust but this is rare. Acute intoxication leads to progressive agitation, confusion and myoclonic jerking. There may be development of generalized tonic–clonic seizures progressing to coma and death. More chronic exposure causes a progressive tremor, incoordination and ataxia with the development of focal epilepsy. Dialysis dementia (Chapter 19) is at least partly brought about by the toxic effects of aluminium in the dialysis fluid and in phosphate binders. Aluminium retention occurs in the uraemic state and progressive cognitive impairment, dysarthria and encephalopathy may develop after several years’ dialysis. The treatment includes de-ionization of the dialysate and avoidance of aluminium-containing phosphate binders. However, aluminium intoxication can occur as a consequence of chelation therapy that actually displaces sequested aluminium from bone and this should therefore be avoided.

Thallium

Exposure to thallium is now relatively rare as its use has been banned in pesticides. There is still an occasional incidence of deliberate exposure by attempted murder or suicide. Acute exposure may lead to an encephalopathy characterized by hallucinations, paranoia and cognitive impairment. Systemic involvement is similar to arsenic in causing abdominal cramps, vomiting and diarrhoea. Alopecia develops after several weeks and Mees’ lines are seen in the nails. There may be a progressive encephalopathy with ataxia, chorea and confusion culminating in cardiac and respiratory failure and coma. Chronic exposure leads to a progressive predominantly sensory axonal neuropathy which is painful and associated with distal sensory loss, weakness and areflexia. Neurophysiology confirms progressive axonal loss. High thallium levels can be detected in blood, urine and hair samples. The treatment is with gastric lavage, laxatives and haemodialysis. Absorption from the gastrointestinal tract can also be reduced by Prussian blue or activated charcoal, both of which bind thallium.

Tin

Tin is extensively used in the manufacture of electronics and in soldering. The inorganic form is not associated with any abnormal neurological features but the organic forms (in particular triethyl tin), which may be inhaled, lead to progressive neurological dysfunction characterized by raised intracranial pressure with headache, apathy, cognitive impairment and hallucinosis culminating in seizures and coma. There may also be behavioural disturbances including emotional lability and cognitive impairment with confusion and disorientation. Abnormal eye movements, papilloedema and a cerebellar syndrome also occur. Blood levels are a poor guide; urine levels may be more reliable. Treatment is by use of chelating agents, plasma exchange and D-penicillamine.

Bismuth

Bismuth is contained in some surgical dressings and is sometimes used in the treatement of peptic ulcers and to bulk stools after colostomy. Excessive intake can lead to a progressive behavioural disturbance including depression, apathy and irritability, culminating in a florid encephalopathy with hallucinosis, tremor, myoclonus, ataxia and dysarthria leading to convulsions and coma. The myoclonus is characteristically stimulus-sensitive and may be multi-focal or generalized. Chelation treatment with dimercaprol is often effective.

Solvents and toxins

CNS dysfunction can occur as a consequence of an accidental exposure to a high dose of industrial solvents or to more prolonged chronic exposure to moderate levels in the workplace or as a drug of abuse. The long-term symptoms of prolonged exposure to solvent vapour include progressive cognitive deficits affecting attention, memory and executive function and causing visuo-spatial disturbance with subsequent cerebellar or motor involvement.

Toluene

Toluene (methyl benzene) is a volatile hydrocarbon solvent used in the manufacture of paints, glues and petrol. Exposure occurs relatively commonly during manufacture or industrial processes and the condition may be unrecognized. However, much of toluene poisoning is attributable to deliberate inhalation, such as in glue sniffing. Toluene is highly lipid-soluble and so crosses the blood–brain barrier readily. It causes CNS demyelination, with secondary neuronal damage (Figure 18.1). It also causes a mixed axonal–demyelinating neuropathy. Acute exposure leads to progressive headache, nausea, vomiting and dizziness. There may be cardiorespiratory symptoms secondary to pulmonary hypertension before the development of cognitive impairment including euphoria, disorientation, memory loss and focal neurological signs such as dysarthria, ataxia and intention tremor with progression to stupor and coma. Long-term exposure is associated with toxic encephalopathy, progressive intention tremor and stimulus-sensitive myoclonus and there may be a progressive optic neuropathy with opsoclonus. MRI scan may show cerebral atrophy or diffuse symmetrical abnormalities in the basal ganglia, thalamus or cingulate gyrus or extensive white matter high signal change. There are elevated urinary hippuric acid levels and blood toluene can also be a valuable guide. Treatment is by removal of the source of the exposure and supportive care.

Trichloroethylene and tetrachlorethylene

Trichloroethylene (TCE) and tetrachlorethylene (perchlorethylene; PCE) are industrial solvents particularly used as degreasers but also in dry-cleaning fluids. Exposure occurs by inhalation, contamination of drinking water or in recreational abuse because of their euphoric effects. Acute toxicity causes encephalopathy characterized by progressive nausea, dizziness and headache leading to disorientation, stupor and coma. Chronic exposure is associated with trigeminal neuropathy causing progressive sensory impairment spreading from the nose in a trigeminal distribution leading to facial and buccal numbness. Weakness of the muscles of mastication and facial expression may then develop with progressive ptosis, ophthalmoplegia, retrobulbar neuritis, optic atrophy and vocal cord involvement. Further exposure leads to a chronic sensorimotor neuropathy with mixed axonal and demyelinating features and progressive impairment of attention, memory and orientation. The level of TCE metabolite trichoIorethanol can be measured to monitor exposure. Treatment is by removal from exposure. Patients who have been acutely exposed should have oxygen administered and be treated with gastric lavage and haemodialysis. Improvement in trigeminal and other cranial nerve involvement is usually incomplete.

Ethylene oxide

Ethylene oxide is used to sterilize heat-sensitive medical equipment and as an alkylating agent in industrial synthesis. It is highly toxic causing a severe progressive reversible encephalopathy. Long-term exposure leads to a sensorimotor axonal neuropathy and mild cognitive change. Improvement generally follows discontinuation of exposure.

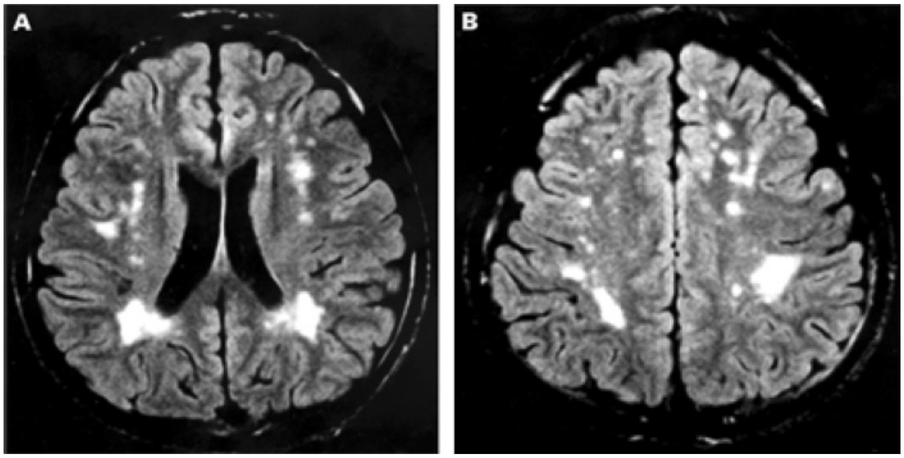


Figure 18.1 Toluene exposure. MRI T1W showing extensive white matter change.

Hexacarbon solvents

Hexacarbon solvents, and in particular n-hexane and methyl n-butyl ketone (MnBK), are neurotoxic and are liberated during petrol production and refining. They are also present in most glues and solvents and are widely abused for recreational reasons. A reversible acute encephalopathy is common in those who take solvents for recreational reasons, leading to euphoria, dizziness, ataxia and progressive cognitive impairments. However, chronic exposure causes a progressive distal sensorimotor axonal peripheral neuropathy associated with autonomic involvement and parkinsonism.

Xylene and styrene

Xylene and styrene are structurally similar to toluene and found in solvents, paints and varnishes. Acute exposure occurs by inhalation or absorption from the skin and may lead to acute encephalopathy with disturbances of cognition, attention and behaviour. Chronic exposure to lower levels can cause mild but progressive disturbance of behaviour, psychomotor performance and visual function.

Carbon disulphide

Carbon disulphide is used as a solvent in varnishes and insecticides, in the manufacture of plastics including rayon and cellophane as well as the vulcanization of rubber. It is a potent neurotoxin with exposure caused by inhalation and oral ingestion rather than by transdermal exposure. Acute exposure to high levels leads to encephalopathy with progressive drowsiness and disruption of behaviour, personality and memory with mood swings, mania, hallucination, depression, psychotic disturbances and memory loss. A similar encephalopathy occurs with chronic exposure but a distal demyelinating sensori-motor peripheral neuropathy may occur and there may also be parkinsonism, retinopathy, optic neuropathy and a small vessel vasculopathy. Blood and urine carbon disulphide levels give a guide to exposure. The treatment is removal from the source of toxicity but no agent is available to neutralize the effects of carbon disulphide which may be present for many years.

Cyanide

Cyanide blocks trivalent iron in cellular respiration enzymes and inactivates cytochrome oxidase. This leads to an immediate cessation of cell respiration with hypoxia and respiratory arrest. Exposure usually occurs as a consequence of deliberate poisoning. However, cyanide poisoning can also occur during accidental smoke inhalation or from ingestion of incorrectly prepared cassava flour (Konzo, see below). Acute exposure affects structures with high oxygen requirements leading to haemorrhage necrosis. Presentation is with dizziness, headache, vertigo and agitation, culminating in seizures, respiratory arrest and death. Chronic ingestion can cause progressive cognitive impairment, parkinsonism and delayed dystonia. MRI shows bilateral areas of hyperintensity in the lentiform and caudate nuclei also the striatum and globus pallidus. Treatment involves immediate administration of 100% O_2 followed by hydroxycobalamin and sodium thiosulphate.

Acrylamide

Acrylamide is used as an adhesive and grouting agent. Inhalation or cutaneous exposure may occur during manufacture or in the polymerization process. Acute high-dose exposure can cause an encephalopathy characterized by confusion hallucinations and drowsiness. More commonly, however, chronic exposure leads to a characteristic progressive sensorimotor axonal neuropathy which initially develops in the lower limbs before affecting the upper limbs. Autonomic involvement is common with hyperhidrosis and dermatitis. There may be a progressive cerebellar ataxia and occasionally pyramidal signs occur. Nerve conduction studies confirm the presence of an axonal sensorimotor polyneuropathy initially affecting large myelinated fibres and biopsy shows distal axonal degeneration.

Allyl chloride

Allyl chloride is used in the preparation of epoxy resins and insecticides. It can cause a mixed motor and sensory distal axonal neuropathy which only recovers after prolonged discontinuation.

Methyl bromide

Methyl bromide is widely used as a refrigerant, in fire extinguishers and as a soil fumigant. Acute exposure causes encephalopathy with progressive convulsion and delirium leading to hyperpyrexia, coma and death. Chronic exposure to lower levels causes systemic features including nausea, vomiting, headache and mucosal irritation before CNS deficits develop which may include progressive speech disturbance and cerebellar ataxia, incoordination and myoclonus. Long-term exposure leads to a distal sensorimotor polyneuropathy, occasionally upper motor neurone signs, and visual disturbance including optic atrophy. Management is supportive but dialysis may be necessary to remove bromide.

Methyl chloride

Methyl chloride is a methylating agent used in the production of lead, rubber or polystyrene foam. Toxicity is associated with inhalation or absorption through the skin. There is CNS depression which may cause headache, dizziness, confusion, speech abnormalities and diplopia with incoordination. Severe prolonged exposure may lead to seizures or stimulus-sensitive myoclonus.

Nitrous oxide

Exposure to nitrous oxide (N_2O) occurs in patients receiving prolonged general anaesthesia or by intentional inhalational abuse. N_2O disrupts B_{12}-dependent pathways and the clinical pattern of toxicity is therefore identical to subacute combined degeneration with extensive spinal cord, brain and peripheral nerve demyelination. Nitrous oxide oxidizes cobalamin and therefore disrupts methionine synthase reduction, necessary for methylation reactions, which are in turn important for production of myelin. N_2O causes a progressive distal sensory neuropathy beginning in the hands with proprioceptive loss secondary to involvement of large sensory nerves and dorsal columns. Progressive spasticity and hyper-reflexia reflecting myelopathy then develops. Nerve conduction confirms slowing of motor and sensory conduction velocities with secondary axonal loss. Vitamin B_{12} replacement may help in the management but this does not always reverse the neuropathy.

Organophosphates

Forty per cent of pesticides contain organophosphates; they are also found in herbicides, as a petroleum additive and a flame retardant. Exposure usually occurs in agricultural settings although ingestion may occur in children or in suicide attempts. Organophosphates inhibit acetylcholinesterase leading to cholinergic toxicity. In acute exposure this is typically manifest within 4 days and resolves over 3–4 weeks. Presentation is with salivation, lacrimation, diarrhoea, urinary frequency, mydriasis, bradycardia, bronchoconstriction and diffuse muscle weakness involving respiratory, bulbar and proximal limb musculature leading to respiratory failure. Acute central effects are also seen causing confusion, dizziness, ataxia, blurred vision and impaired memory culminating in seizures and coma. Chronic exposure ('sheep dipper flu') is characterized by transient symptoms including headache, rhinitis, pharyngitis and myalgia. However, a longer term mild impairment of cognitive and memory functions occasionally occurs. Prolonged exposures may also lead to a late onset sensorimotor axonal peripheral neuropathy and occasionally ataxia and upper motor neurone involvement with spasiticity. Organophosphates are easily absorbed through the skin and therefore it is important that those with potential exposures use protective masks, gloves and appropriate clothing. The skin should be carefully washed following exposures and it is essential to maintain the airway because of the risk of aspiration. Prolonged treatment with atropine, pralidoxime or obidoxime and benzodiazepines may be necessary.

Carbon monoxide

Carbon monoxide (CO) is clear, colourless and odourless. It is commonly used in attempted suicide but exposure also occurs from leaking car exhausts or incorrectly installed domestic gas-powered boilers. Occasional exposure may occur in miners and gas workers. CO has a greater affinity for haemoglobin than does oxygen itself and therefore binds preferentially to oxygen-binding sites to form carboxyhaemoglobin. This limits dissociation of oxygen in the tissues resulting in relative tissue hypoxia. Carboxyhaemoglobin also inhibits oxygen binding and oxidative phosphorylation in the mitochondria further exacerbating functional hypoxia in tissues with a high metabolic demand. Acute exposure causes headache, dizziness, confusion, disturbance of consciousness and behavioural change. Visual disturbance and progressive shortness of breath develop rapidly with subsequent loss of consciousness, seizures, coma and cardiac arrest. Exposed individuals can have pink/red skin, or may be cyanosed. Prolonged acute intoxication is fatal in 2–25% of exposed individuals. A high proportion of survivors have residual neurological features including extrapyramidal signs. Patients with initial transient choreiform movements may develop progressive parkinsonian features, progressive dystonia and urinary incontinence. A delayed onset encephalopathy may develop after a period of apparent partial or complete recovery with cognitive and personality impairment with memory dysfunction, apathy, mutism and the progressive development of vegetative features. There may be elevated levels of carboxyhaemoglobin and MRI shows diffuse symmetrical high intensity white matter change involving caudate and bilateral pallidal necrosis. Treatment of acute exposure is by removal from the source and the provision of 100% oxygen. Hyperbaric oxygen may enhance recovery from acute symptoms. However, the prognosis for neurological recovery after CO exposure is poor.

Insidious chronic low-grade exposure to CO may be associated with industrial exposure or badly ventilated and faulty household heating appliances. The syndrome of chronic occult CO poisoning is manifest as headache, fatigue, dizziness, paraesthesiae, visual disturbance with chest pain and palpitation associated with ventricular arrhythmias. The diagnosis of low-grade exposure depends on recognition of the syndrome and demonstration of elevated levels of carboxyhaemoglobin. Management depends on identifying the source of CO and prompt removal. Oxygen therapy, as discussed above, may be necessary.

Marine toxins

Marine toxins are difficult to detect as they are often without colour, taste or odour. Furthermore, most are unaffected by cooking, freezing or salting.

Ciguatera

Ciguatera toxin (ciguatoxin) occurs in reef fish (e.g. snapper or barracuda) who consume an apophytic dinoflagellate which elaborates the toxin. The toxin causes voltage gated sodium channels to open. Poisoning leads to the rapid development of acute abdominal cramp, nausea, vomiting and diarrhoea. Peri-oral, limb and trunk paraesthesiae develop 12–48 hours after ingestion of contaminated fish. In the most severe cases there is a characteristic cold allodynia ('temperature reversal'). Cranial nerve palsies, polymyositis or a rapidly progressive sensorimotor and autonomic polyneuropathy affecting bulbar and respiratory muscles can occur. This progresses to limb weakness, flaccid quadriplegia and respiratory muscle impairment. Although the condition generally resolves spontaneously within a few days, fatalities are caused by respiratory insufficiency and cardiac dysfunction may occur. Bioassay of the toxin is possible. Treatment is supportive.

Tetrodotoxin

Tetrodotoxin (TTX) occurs in the liver and ovaries of puffer fish and toad fish from the family Tetraodontidae and also occurs in some types of crabs. TTX blocks voltage-gated sodium channels at nanomolar concentrations. Onset is with numbness of the lips and tongue followed by worsening paraesthesiae in the face and limbs with a sense of floating or light-headedness and systemic features including gastrointestinal disturbance. With ingestion of large amounts of TTX there is worsening neuromuscular paralysis involving the limbs, trunk, cranial nerves and respiratory muscles leading to death if artificial ventilation is not instituted. Supportive treatment is successful in most cases because the condition is fully reversible, although it is important to note that patients can be fully conscious in spite of total paralysis. Atropine treatment may be necessary to treat bradycardia.

Scombroid

Scombroid poisoning is common as it is caused by poor storage of tuna and similar fish. Toxicity differs from the other marine toxins as it has a histamine-like effect. The onset is rapid and resembles an acute anaphylactic response with pruritus, throbbing headache, erythema, urticaria, paraesthesiae and palpitation; poisoning tends to be self-limiting. Treatment is with intravenous histamine receptor blockers and supportive care.

Shellfish

Shellfish toxicity may be caused by secondary infectious agents such as *Vibrio cholerae* and hepatitis A and occurs with bi-valve molluscs including clams, mussels, scallops and oysters. Saxitoxin is a heat-stable water-soluble toxin that is concentrated in shellfish which also acts by blocking voltage gated sodium channels. There is a rapid onset of paraesthesiae, particularly peri-orbital, and subjective limb weakness. There may be severe respiratory involvement including the diaphragm with significant mortality. Neurotoxic shellfish poisoning is caused by brevetoxins which cause depolarization of excitable membranes with persistent activation and repetitive firing of nerve and muscle. There is simultaneous onset of gastrointestinal and neurological symptoms including tremor, dysphagia, pupillary paralysis and hyporeflexia. Amnestic shellfish poisoning is caused by the toxin domoic acid which stimulates kainate-type glutamate receptors and has a toxic action on the limbic system leading to antegrade and retrograde amnesia, seizures, myoclonus and coma. Systemic symptoms include labile blood pressure, cardiac dysrhythmia and myoglobinuria. The syndrome may improve gradually over 3 months but residual amnestic deficits occur.

Other biological toxins

Snake venom

Snake venom from many members of the Elapidae family, which includes the banded krait and sea snakes, contains toxins that cause neuromuscular junction (NMJ) blockade resulting in a myasthenia-like syndrome, particularly affecting the muscles of neck flexion and the ocular, bulbar and proximal limb muscles, occasionally leading to respiratory paralysis. Onset is often with local pain, swelling and erythema in the region of the bite with local lymph node involvement. The onset of systemic symptoms depends upon the site of the bite and the species, but over 1–12 hours muscle fasciculation, weakness and hypotension can develop with eventual shock.

Presynaptic NMJ dysfunction occurs with β-bungarotoxin envenomation by banded kraits while α-bungarotoxin causes an additional post-synaptic NMJ blockade. Snake bites generally cause death not because of the paralysis but because of the systemic effects of proteolytic toxins acting on blood constituents and tissues. Nevertheless, the neurological features can aid diagnosis and choice of appropriate anti-venom.

Spiders

The female black widow spider produces a neurotoxin (α-latrotoxin) which triggers massive spontaneous neurotransmitter release, from the NMJ as well as other synapses. There may be intense pain in the region of the bite with a characteristic erythematous target lesion. This is followed by the development of involuntary spasms in the abdominal muscles which spreads to involve the limbs. The funnel-web spider, indigenous to parts of Australia, produces a toxin that affects sodium channels and causes a severe dysautonomia, piloerection, sweating and diaphragm involvement culminating in respiratory arrest. Treatment is by supportive care in intensive care with anti-venom if available. Muscle spasm is treated with benzodiazepines.

Scorpions

Scorpions elaborate a toxin that has both presynaptic and postsynaptic effects. These may lead to local symptoms followed by the development of progressive severe autonomic impairment with muscle fasciculation and progressive bulbar, respiratory and cardiac involvement. Occasionally, encephalopathy may occur secondary to CNS involvement.

Ticks

Ticks cause a rapidly developing, progressive flaccid motor weakness affecting ocular, bulbar, respiratory and limb musculature because of presynaptic inhibition of acetylcholine. It is essential for the tick to be removed immediately.

Fungal poisons

Fungal poisons are highly diverse, and neurotoxic compounds occur in several of the most toxic species. Some members of the Amanitae family such as the fly agaric (*Amanita muscaria*) contain molecules that act at GABA, glutamate and acetylcholine receptors (muscimol, ibotenic acid and muscarine). However, the high fatality associated with death cap (*Amanita phalloides*) ingestion is mainly associated with amatoxin, which inhibits mRNA synthesis and leads to hepatic and nephrotic toxicity. Some members of the Psycilocybe family are used recreationally because of their psychoactive effects. Psilocybins are structural analogues of serotonin and produce LSD-like effects with euphoria, hallucination, tachycardia and eventually seizures.

Lathyrism

Lathyrism occurs in countries where the chickling pea (grass pea) *Lathyrus sativus* is grown, and generally only under conditions of food deprivation. It is may be caused by the neurotoxic amino acid β-N-oxalylamino-L-alanine (BOAA), which acts as an agonist at the AMPA subclass of glutamate receptors. There is prominent degeneration in Betz cells of the motor cortex and pyramidal tracts. The condition develops with an insidious onset of gait unsteadiness and development of a spastic paraparesis with normal sensory examination. There is no involvement of cognition or cerebellar function. A peripheral sensory neuropathy, which is predominantly demyelinating, may occur in a minority of patients. A related toxin, beta-methylamino-L-alanine (BMAA) is present in the fruit of the cycad palm, and has been implicated in the amyotrophic lateral sclerosis–parkinsonism–dementia complex amongst the Chamorro population. However, it remains unclear whether consumption of this toxin can account for the epidemiological evidence.

Konzo

Konzo occurs in epidemics in East and Central Africa. It affects children above the age of 3 years and women of childbearing age, causing sudden-onset symmetrical non-progressive permanent spastic paralysis, predominantly affecting the lower limbs but spreading to involve the upper limbs and the cranial nerves. The pathology resembles lathyrism with involvement of cortical Betz cells directed towards the lower extremities and their corresponding corticospinal tracts. It is believed to be associated with high dietary levels of cyanide caused by the intake of poorly prepared bitter cassava, particularly if there is protein malnutrition, but the aetiology of Konzo continues to be debated.

Methanol and ethanol

Methanol and ethanol are considered below.

Botulism

Botulism is considered in Chapter 8.

Radiation-induced neurological disease

Exposure to radiation occurs naturally but this is usually low intensity and carries few risks. Increased levels are associated with exposure to occupational or therapeutic radiation and, rarely, to nuclear weapons. Radiation can be divided to non-ionizing and ionizing. Non-ionizing radiation (e.g. ultraviolet, infra-red, microwaves, radio waves, laser radiation and visible light) has low energy and is therefore unable to break chemical bonds and cause ionization; thus, injury is caused by local heat production and is generally mild, although damage to retinal and optic nerve fibres may occur. However, ionizing radiation is considerably more serious. This radiation is caused by high energy particles or electromagnetic waves (X-rays and gamma rays) which can break chemical bonds and therefore produce ionization within tissues leading to DNA damage and mutation. Ionizing particulate radiation is caused by α particles, electrons, neutrons or protons. Alpha particles (composed of two protons and two neutrons) are produced by uranium, radium and polonium. They lead to high levels of ionizing radiation but are usually blocked by paper or clothing and are therefore only toxic if ingested or inhaled. Beta particles are high energy electrons emitted from decaying isotopes of strontium 90 which are commonly used to generate X-rays and radiotherapy. Toxicity also occurs with ingestion. High energy neutrons are only produced with nuclear fission but are a serious radiation risk following detonation of a nuclear reaction or if a reactor becomes critical. Proton exposure also occurs naturally from cosmic radiation.

The early effects of radiation, seen after exposure to large doses delivered over a short period of time (>1 Gy), affect rapidly dividing tissues including skin, bone marrow and gut epithelium. The onset is with prodromal gastrointestinal symptoms before the condition manifests with bone marrow suppression, loss of intestinal mucosal cells leading to bowel disturbance and sepsis, and finally cerebrovascular involvement. Management involves meticulous decontamination at the site of exposure and supportive care with transfusion and treatment of sepsis.

Late toxicity following accidental or therapeutic exposure to radiation is usually seen in organs with slowly dividing cells such as the CNS, kidney and liver, causing radiation necrosis. The characteristic delayed complication is malignancy, particularly of the thyroid gland, breast or leukaemia.

Therapeutic radiation

Therapeutic radiotherapy creates ionized oxygen which reacts with cellular DNA. Healthy cells have a greater ability than tumour cells for DNA repair and therefore the cumulative effects of unrepaired DNA result in cell death (apoptosis of tumour cells while healthy cells are more able to repair themselves). Acute complications of therapeutic radiotherapy include encephalopathy which can occur during or up to 1 month after radiotherapy has been commenced. It is associated with headaches, nausea, changes in mental state and symptoms suggestive of increased intracranial pressure because of breakdown of the blood–brain barrier and secondary cerebral oedema. The more acute effects of therapeutic radiotherapy also include hypersomnolence, encephalopathy, memory disturbance and there may also be gastrointestinal symptoms. The MRI shows increased oedema with contrast enhancement which may resolve over several months. The condition is caused by damage of the blood–brain barrier and is steroid responsive. (See Chapter 20.)

Early-delayed radiation encephalopathy

Early-delayed radiation encephalopathy develops 1–4 months after radiotherapy and is caused by injury to oligodendroglia producing demyelination and vasogenic oedema. This may present with somnolence, decline in long-term memory and encephalopathy. There may also be brainstem involvement with diplopia, nystagmus, dysarthria and ataxia. This form of radiation encephalopathy resolves over several weeks but occasionally may progress to profound encephalopathy, coma and death. Subacute encephalopathy may also be associated with a myelopathy and a transient brachial plexopathy.

Late-delayed radiation encephalopathy

Late-delayed radiation encephalopathy develops several months or years after cranial irradiation and is associated with diffuse cerebral atrophy, focal radiation necrosis or secondary vascular change. The pathological findings are of demyelination. There may also be signs of raised intracranial pressure. The patient presents with cognitive decline, personality change and gait disturbance developing 6–18 months or more after total brain irradiation. There may be a more indolent intellectual impairment leading to dementia. Delayed effects of radiotherapy also include endocrine dysfunction because of hypothalamic impairment, optic neuropathy, progressive cranial neuropathy or chronic progressive myelopathy. The incidence of delayed radiotherapy effects is related to total radiation dosage and the size of fractionated doses. A total dose of <5500 Gy carries a 5% chance of developing radiation necrosis. Risk is increased with a higher daily dosage, if there has been concurrent chemotherapy or if there are underlying vascular risk factors. It can be extremely difficult to distinguish brain radiation injury from the effects of brain tumours by conventional imaging. The hypometabolic state of radiation necrosis may be reflected in dynamic imaging such as FDG-PET. Brain biopsy will show extensive necrotic tissue without predominance of malignant cells. There is involvement of the white matter with loss of oligodendrocytes and demyelination. There may also be thickened vessels with endothelial proliferation, fibrosis and moderate infiltration of lymphocytes and macrophages. (See Chapter 20.)

Transient radiotherapy myelopathy

Transient radiotherapy myelopathy usually occurs within the first 6 months of treatment, particularly to the cervical spinal cord, although it may continue to develop for 2 years after treatment. It is most commonly seen in patients treated for lymphoma or neck and thoracic neoplasms. Presentation is with mild sensory impairment including Lhermitte's phenomenon. The condition itself is self-limiting and relates to demyelination in the posterior columns. Chronic, usually progressive, myelopathy is a delayed syndrome which develops >1 year after radiotherapy or tumours in the head and neck, cervical or mediastinal region. Focal neurological deficits related to spinal cord involvement include progressive sensory impairment in the lower limbs followed by progressive myelopathy. There may be a transverse myelitis or Brown-Séquard syndrome with sphincter disturbance. Treatment is with corticosteroids but this only leads to a temporary improvement and there is generally secondary necrosis and atrophy of the cord because of vasculopathy.

Radiation plexopathy

Plexopathy can affect the brachial or lumbar plexus and follows radiotherapy in these regions. It is important to distinguish the development of progressive plexopathy from direct neoplastic involvement of the plexus. The onset is characterized by paraesthesiae and dysaesthesiae with pain and progressive atrophy and weakness developing over several months. It develops 1–3 years or longer after radiotherapy and is particularly associated with high doses of radiotherapy (>6000 Gy), large daily fractionations, lymphoedema, induration of the supraclavicular fossa and myokymia on electromyography (EMG). The condition seems to be due to small vessel damage and fibrosis; it responds poorly to steroids. Positron emission tomography (PET) imaging of the brachial plexus may distinguish malignant infiltration from radiotherapy induced plexopathy.

Radiation administered to the neck can also accelerate the development of carotid artery atherosclerosis. This may develop as early as 1 year after treatment but is often delayed by 10 years or more. It is associated with a high treating dose and daily fractionated dose. Cerebral ischaemia may be caused by atherosclerotic embolization to the brain or haemodynamically significant arterial stenosis. Histologically arterial damage cannot be distinguished from typical atherosclerosis but it occurs in the radiotherapy field.

Lightning and electrical damage to the nervous system

Fifty people are struck by lightning in the UK each year, usually with some three fatalities. This compares with 100 fatalities in the USA. For injuries related to technical electricity (at work and at home), the UK annual estimate is approximately 3000 incidents with 30 fatalities. There are some 1500 deaths from electrocution annually in the USA.

Mechanisms of lightning and other electrical damage

Lightning: initiation and pattern of contact

Intra-cloud lightning is the most common form of lightning, but it is cloud-to-ground lightning that causes human injury. Usually, a highly branched discharge, known as the stepped leader, appears below the cloud base and heads toward the ground at a speed of 10^6 m/s. When the tip of the leader approaches within 30 m of the ground, the induced electric field produces an upward connecting discharge, usually from the nearest tallest object(s). When the two discharges meet, the first return stroke begins; this is an intense wave of ionization that propagates up the leader into the cloud at close to the speed of light. This is followed by a series of further ionizing strokes between the cloud and the ground each lasting some 500 ms with 40–80 ms gaps. These gaps are long enough to allow for retinal resolution of the individual strokes – which is why lightning is seen to flicker. The repeated earthbound strokes do not always follow the path of the initial leader, which is why lightning can appear forked. The large current of the return stroke causes the air in the surrounding channel to heat up to about 30,000°K in a microsecond, the channel pressure rises to 20 atmospheres or more; the decay of this pressure wave is heard as thunder.

Although the electrical forces associated with lightning strike are enormous (10^6 V, 30,000 amps), the damage caused to a person struck is limited by the very short duration of the passage of current. In contrast, in accidental electrical injury, the power sources are much less, but contact can last for seconds or even minutes leading to severe thermal injury of tissues in and around the current path.

The prelude to a strike, familiar to many mountaineers, is the build-up of atmospheric charge with buzzing of metallic equipment, skin tingling and hair standing on end. This is signal for immediate evacuation from prominent features such as a summit or crest of a ridge, if this is feasible. It is unusual for lightning strikes to occur in aircraft, cars or ships at sea because these vehicles act as 'faradic cages'; that is, containers made from a conductor that shields its contents from external electric fields. Because the conductor is an equipotential there is no potential difference within the container.

A major factor that determines injury in lightning strikes is whether the heart or CNS is involved in the current path (either can result in cardiorespiratory arrest), this in turn depends on the way the strike reaches the subject.

1 Direct strikes are the most damaging as the head is usually involved.

2 Side flash occurs when lightning strikes a nearby object such as a tree, and the current arcs to flow through the subject.

3 Ground current injuries are caused by lightning striking the ground near the subject; as the current dissipates, it reaches the subject and passes through them, usually via the legs if they are standing.

4 Most indoor injuries are minor and occur when the subject is shocked by current dissipating along telephone or other wiring.

Many people can be injured at the same time as all of the above mechanisms of current transfer can occur in a single strike; at Ascot racecourse, UK, in 1956, 46 people were injured, two of them fatally.

Electrical injuries: high and low-voltage

Electrical injuries are usually categorized on the basis of the voltage exposure: high (≥1000 V) or low. Low-voltage injuries usually result from exposure in the home, are relatively common but rarely severe (although death can occur from contact with as little as 25 V). High-voltage injuries usually affect those whose occupations bring them into contact with high-tension power lines or electrified rails. Members of the public may be involved in accidents that bring them into contact with these sources – children, anglers carrying their rods, those erecting or using aerials, parachutists and those attempting deliberate self-harm. High-voltage exposure is the cause of some 70% of electrical injuries and death. The voltages and currents associated with electrical exposure are much less than with lightning; however, the period of exposure is longer which magnifies the heating effects of current passage through the body leading to deep tissue necrosis, a complication rarely encountered in lightning strikes. Alternating current can increase this effect if tetanic contraction is induced in flexor muscles of the grasping hand, with periods of exposure approaching a minute or beyond in some cases.

Nervous system complications of lightning and electrical injury

Neurological sequelae can be split into four categories: immediate and transient (IT), immediate and prolonged/permanent (IP), delayed and progressive (DP), and secondary trauma caused by lightning or electrical exposure (e.g. head or spinal injury caused by falls, usually secondary to a loss of consciousness). Complications are generally shared by both types of exposure.

Transient loss of consciousness is the most common symptom associated with both types of electrical exposure, occurring in 70–80% of patients. Confusion, amnesia, paraesthesiae and limb weakness are also common IT symptoms. A specific IT syndrome said to be pathognomic of lightning strike is known as keraunoparalysis (*kerauno*, Greek for thunderbolt; literally, 'smasher'). This is sometimes known as Charcot paralysis; he provided the first description – of short-lived complete lower limb paralysis with spared sphincter function and marked vasoconstriction with limb coolness, lividity and peripheral cyanosis. The symptoms abate over hours or, rarely, days. The pathophysiology is poorly understood. This syndrome should be differentiated from the much rarer true spinal cord syndromes that complicate lightning or electrical injury, which are usually of the IP or DP type.

The neuropathological mechanisms that result in IP or DP symptoms are not fully understood, but probably comprise a mixture of thermal and non-thermal effects of current passage through affected tissues culminating in cell membrane breakdown. Thermally driven cell membrane damage occurs at temperatures as low as 43°C, although exposure needs to be for 4 hours or more to cause thermal disruption of the bilipid layer. Non-thermal mechanisms include electroporation, a process driven by supraphysiological rises in transmembrane electric potential that causes permanent holes in the cell membrane leading to fatal loss of the ionic gradient. Micropathological CNS lesions vary and include haemorrhage (both gross and petechial), neuronal cell death, myelin breakdown and glial proliferation. Cerebral oedema is seen in cases complicated by hypoxic brain injury secondary to cardiopulmonary arrest. The three most reported DP syndromes affect motor neurones, basal ganglia and the cord. Stroke-like syndromes (particularly venous sinus thrombosis), seizures, extrapyramidal syndromes, isolated cerebellar dysfunction (rare) and spinal cord syndromes at any level (also rare) are all described.

Delayed syndromes are the least common. There is often doubt over any causative link, especially as the time since exposure can be many years. This is well illustrated by a study of psychological morbidity in a series of 165 patients with chronic sequelae of lightning and electrical injury. The mean symptom lag from time of exposure was 4.5 years; the majority of the symptoms reported were suggestive of depression.

There is even less evidence for IP or DP syndromes affecting the peripheral nervous system causing a mononeuropathy or polyneuropathy, with the exception of direct thermal damage causing full-thickness burns through individual nerves. Complex regional pain syndromes are also described and are hard to evaluate.

Non-nervous system complications of lightning and electrical injury

Cardiac

Cardiopulmonary arrest is the most common cause of death in lightning and electrical injuries. Although this can be neurogenic it is usually caused by the direct effect of current passing through the heart leading to asystole or ventricular fibrillation. Cardiopulmonary resuscitation in these circumstances is often much more successful than out-of-hospital arrests from other causes.

Skin and muscle damage

Fern-shaped superficial cutaneous burns are sometimes seen following lightning strikes; these heal, but discoloration can persist for some years, or even permanently. Lightning rarely causes major skin or deep tissue burns; however, electrical injury, especially of high-voltage type, can be devastating to deep tissues. It is not possible to predict the amount of deep tissue injury from the overlying skin involvement. Striated muscle is particularly sensitive to AC current and high-voltage exposure is often complicated by rhabdomyolysis, subsequent renal failure, compartment syndromes and surgical amputation following overwhelming limb damage. Cataracts complicate lightning and electrical injuries that involve the head and neck in the current path, including lightning strikes that dissipate along telephone wires.

Management

Initial management includes basic resuscitation and CPR. All patients suffering lightning strike or high-voltage electric injury require transfer to hospital for appropriate therapy and, in some cases, ECG monitoring. Asymptomatic patients with low-voltage injuries in the absence of nervous system, cardiac or skin involvement need not be admitted. The neurologist, like members of other specialist teams, is most likely to be called upon to help with patients with moderate to severe injuries following lightning or electrical injury. There is no good evidence base for particular treatment of neurological symptoms caused by electrical current exposure; symptoms should be treated on their own merits.

Heat stroke

Heat stroke is present if the core body temperature exceeds 40°C (104°F). It may occur either as a result of vigorous and prolonged exertion or during excessively hot weather, when it affects those who have difficulty with heat regulation including children, the elderly or those with chronic medical problems causing impairment of the mechanisms of heat loss (e.g. dermatological disease or following ingestion of anticholinergic drugs).

In non-exertional heat stroke, presentation is usually with progressive impairment of consciousness manifest as irritability, confusion, delusions and hallucinations culminating in coma. There is usually anhidrosis and patients may develop hallucinations, cranial nerve abnormalities, early cerebellar dysfunction (ataxia, tremor and dysarthria), seizures and opisthotonus or the development of cerebral oedema with decerebrate posturing and status epilepticus. Systemic involvement leads to a hyperdynamic circulation with tachycardia and postural hypotension (caused by vasodilatation of cutaneous vessels and venous pooling), dehydration, congestive cardiac failure, systemic inflammatory response syndrome, multi-organ failure, myocardial damage and rhabdomyolysis.

Following exertional heat stroke, non-specific symptoms of heat exhaustion are often unrecognized before impairment of consciousness develops – these include fatigue, weakness, nausea, vomiting, abdominal pain, muscular cramp, headache and syncope. Predisposing factors include exercise in inappropriate clothing, e.g. wet-suits, viral illness, obesity, dehydration, poor physical fitness, excessive alcohol and illicit drugs, e.g. cocaine and amphetamines. When heat stroke becomes established the clinical features are identical to those patients with non-exertional causes.

Treatment is with rest, removal from the hot environment and correction of dehydration and electrolyte disturbances. Gentle cooling and oral rehydration is adequate in mild cases but in more severe cases ventilatory support, intravenous fluids and intensive monitoring of fluid, electrolyte balance and cardiac and neurological function is necessary. Cold gastric or peritoneal lavage or the use of cooling devices or controlled hypothermia may be of value. Iced water immersion is an efficient form of reducing the core temperature rapidly but is usually impracticable in patients with impaired consciousness and highly uncomfortable for those patients who are awake. Evaporation techniques are safer and as effective as immersion.

A poor prognosis is suggested by the development of lactic acidosis, acute renal failure, hypercalcaemia, coagulopathy or prolonged coma (>4 hours). Muscle necrosis may lead to a grossly elevated creatine kinase (CK) level. Death occurs as a consequence of cerebral oedema and herniation. It is essential to recognize persons at risk of heat stroke and to ensure they are not exposed to excessive heat and maintain adequate fluid replacement.

Hypothermia and non-freezing cold injury

Accidental hypothermia is the unintentional decline in core temperature below 35°C (95°F). Primary hypothermia is caused by exposure to cold; secondary hypothermia occurs when a disease causes failure of thermoregulation (e.g. CNS tumour leading to hypothalamic impairment, exposure to toxins or neurodegenerative disorders). Hypothermia causes bradycardia because of decreased depolarization of cardiac pacemaker cells which is not mediated by the vagus and is resistant to therapies such as atropine. Hypothermia progressively depresses the CNS. With mild hypothermia there is confusion, lethargy, loss of fine motor coordination with ataxia, dysarthria and slowed reflexes. Severe hypothermia (<28°C) is characterized by rigidity, areflexia, reduced consciousness and eventually coma. At core temperatures <35°, brain electrical activity becomes abnormal and below 20°C the EEG can be flat and consistent with brain death.

Management is aimed at preventing dysrhythmias, particularly ventricular fibrillation, ensuring adequate oxygenation and initiating external and core rewarming using warm intravenous fluid, abdominal lavage and, if necessary, cardiopulmonary bypass. Intensive intervention is indicated, even in those who appear dead. Hypothermia is neuroprotective; some patients may recover completely.

Non-freezing cold injury describes persistent painful and autonomic symptoms, usually in the feet, following exposure to temperatures approaching 0°C. Symptoms may last many years are occasionally permanent.

Diving

The effects of diving relate to the high pressure environment and the consequences of decompression. Barotrauma occurs when divers descend beyond a depth of 100 m breathing gas mixtures of helium and oxygen. Damage occurs because the volume of a gas decreases under a high pressure (Boyle's law). At depth, the body space fails to equate with the external environmental pressure. Barotrauma can also affect the middle or inner ear, sinuses, teeth or gastrointestinal tract causing headache, facial pain, vertigo, hearing loss and abdominal pain. Direct high pressure injury to the CNS leads to a progressive rest or intention tremor, myoclonus, hyper-reflexia and transient cognitive and memory disturbance.

Decompression sickness

Decompression sickness (DCS) occurs because the solubility of a gas increases under high pressure (Henry's law). Therefore, nitrogen dissolved in the tissues at depth will be released as gas as the diver ascends to a higher atmospheric pressure. DCS ('the bends') occurs when surfacing to a lower pressure causes the release of air bubbles (usually composed of nitrogen) into the bloodstream and tissues. DCS usually develops within 2 hours of surfacing but may be delayed by up to 36 hours. DCS type I is characterized by limb and joint pain, while DCS type II causes cardiorespiratory impairment and involvement of the CNS because of direct mechanical effects of the air bubbles or due to arterial gas emboli. Cerebral DCS usually involves the arterial circulation leading to alteration in the level of consciousness, weakness, headache, gait disturbance, fatigue, diplopia or visual loss. There may be acute hemispheric dysfunction causing hemiparesis, aphasia and hemianopia and/or progressive encephalopathy, coma and death. Pathologically, the condition is characterized by oedema, haemorrhagic infarction and axonal degeneration with demyelination. Occasionally, brainstem involvement may lead to vestibular disturbance. Spinal cord DCS presents with partial myelopathy that localizes to the thoracic cord although the level may vary from C4 to L1. The onset is often acute (<3 minutes of surfacing) with the development of weakness, paraesthesiae and numbness of the legs with early bladder involvement. The severity may vary from mild sensory involvement to dense limb weakness. MRI may show high signal lesions on T2-weighted imaging.

The treatment of established DCS requires the urgent provision of hyperbaric oxygen. While most cases resolve the prognosis remains uncertain and residual deficits occur in some patients.

Arterial and venous gas emboli

Arterial gas emboli formed in the tissues can also enter the venous circulation. There is a particular risk, even following a shallow dive, if there is a patent foramen ovale with a right to left cardiac shunt.

Altitude medicine

Acute mountain sickness and cerebral oedema

Acute mountain sickness (AMS) is a relatively common condition occurring in unclimatized subjects ascending rapidly to 2500 m or above. It is usually self-limiting with appropriate management. A small proportion of patients develop the far more serious complications of cerebral and pulmonary oedema (usually >4000 m). AMS is manifest as headache, fatigue, weakness, dizziness, difficulty sleeping, and gastrointestinal symptoms such as anorexia, vomiting and nausea. A chronic form may occur as a consequence of persisting hypobaric hypoxia causing persistent malaise and headache. AMS may be prevented by slow ascent (height should be gained slowly above 2500 m at the rate of 300–500 m/day) carrying little and with frequent rests. Symptomatic treatment includes analgesics and antiemetics. Acetazolamide, a carbonic anhydrase inhibitor, is also widely used for prevention but is associated with significant toxicity and it is recommended that a therapeutic trial should be undertaken at sea level before use. Dexamethasone may also help.

With continued ascent, pulmonary and cerebral oedema may occur. On a 6000-m peak there is only 50% of sea level O_2 and the arterial PO_2 is approximately 50 mmHg. Brain perfusion (cerebral blood flow) increases at even modest altitude to 3500 m in response to hypobaric hypoxia and can lead to the development of cerebral oedema. Presentation may be gradual or acute. Onset is usually with severe headache and progressive ataxia. There may be neuropsychological effects including impairment of short-term memory, defects in verbal fluency and cognitive function with the development of hallucinations. Papilloedema and focal signs including cranial nerve palsies, hemiplegia and seizures may develop and impaired consciousness evolving from drowsiness to coma may develop over 12–72 h. Sudden devastating altitude-related cerebral oedema may develop unpredictably at extreme altitude (usually >7000 m) in climbers who have been apparently well acclimatized (Figures 18.2 and 18.3; Plates 18.1–18.5).

Investigations are not usually possible but where MRI has been undertaken in high altitude cerebral oedema there are features of brain oedema and posterior reversible leucoencephalopathy and changes in the splenium of the corpus callosum. In fatal cases there are ring micro-haemorrhages in the brain, arterial and venous thrombosis.

It is essential to have a high index of suspicion for these conditions. Exercise should be avoided and the patient should descend as soon and as fast as feasible – most deaths occur because the subject remains at a high altitude. Treatment is with 8 mg dexamethasone by mouth or injection and then 4 mg dexamethasone 4-hourly for several days before gradually weaning the dose over a week. Oxygen inhalation (6 L/minute initially) or hyperbaric oxygen administered by a portable pressure chamber should be used if available (Table 18.2).

Retinal haemorrhages are common at >5000 m but rarely cause visual loss and usually resolve spontaneously. They are not a manifestation of high altitude cerebral oedema. Cerebral infarction manifest as stroke or transient ischaemic attack (TIA) occurs more commonly than expected and is probably related to dehydration and polycythaemia secondary to hypoxia.

High altitude pulmonary oedema

High altitude pulmonary oedema is also caused by hypoxia but is often less obvious than cerebral oedema. It is manifest as breathlessness at rest, dry cough, dyspnoea, crackles in the lung bases and the production of copious pink frothy sputum. Once again the patient must be evacuated immediately to a lower altitude and rapidly provided with oxygen inhalation at a minimum of 2 L/min. Acetazolamide 250 mg 6-hourly may also be valuable and nifedipine and prophylactic salmeterol have also been used (Figure 18.3).

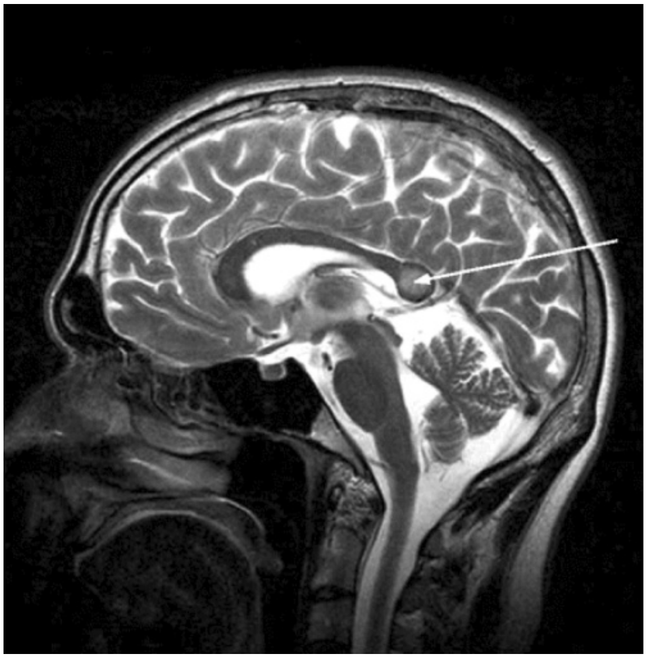


Figure 18.2 High altitude cerebral oedema. T2-weighted MRI scan showing oedema of splenium of corpus callosum. (From Clarke 2006, courtesy of Dr Sui Wong, with permission from the publishers.)

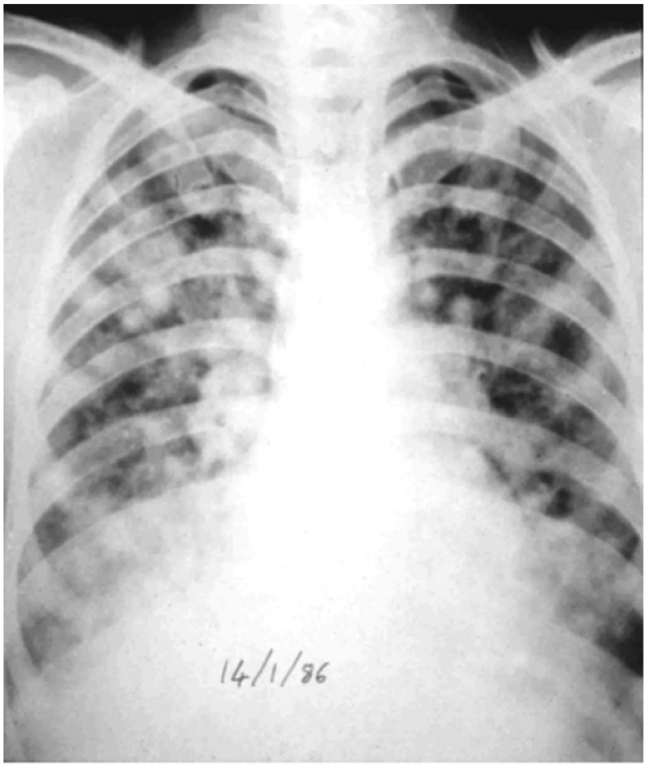


Figure 18.3 Chest X-ray showing high altitude pulmonary oedema. (From Clarke 2006, with permission from the publishers.)

Table 18.2 Treatments for severe forms of altitude illness. (From Clarke 2006, with permission.)

Manoeuvre/drug	Regimen	Comment
Descent	250 m descent often helpful	Essential, if possible
Dexamethasone	8 mg + 4 mg every 6 h (iv, im, oral)	Often helpful in minutes, used primarily for brain oedema
Nifedipine	10 mg + 20 mg sustained release every 12 hours	Mainly for pulmonary oedema
Oxygen	2–6 L/min by mask or cannula	Always helpful, calming
Portable chamber (Plate 18.4)	2–4 psi for 2–3 hours	Never truly portable/claustrophobia

im, intramuscular; iv, intravenous.

Neurobiological weapons

Biological weapons, although simple to produce, may be highly potent and difficult to detect. Indeed, recognition that a chemical or biological attack has occurred may be extremely difficult because of the delay before clinical manifestations become apparent. Diagnosis may depend on recognizing a pattern of clustering or atypical illness in animals or humans, possibly occurring at an unusual age. Potential biological agents of terrorism are listed in Table 18.3.

Table 18.3 Potential biological agents of terrorism.

Bacteria
- *Bacillus anthracis*
- *Brucella suis*
- *Francisella tularensis*
- *Rickettsia*
- *Salmonella typhi*
- *Shigella*
- *Vibrio cholerae*
- *Yersinia pestis*

Viruses
- Encephalomyelitis
- Engineered viruses
- Smallpox
- Viral haemorrhagic fever

Chemical agents
- Hydrogen cyanide
- Chlorine
- Mustard gas
- Nerve agents
  - Tabun
  - Sarin
  - Soman
  - VX
  - VR
- Ricin

Toxin
- Aflatoxin
- Botulinum

Mycotoxins
- Tetrodoxine
- Saxitoxin

Modes of release

Aerosol release of infectious particles is the most efficient form of dissemination and can be accomplished relatively easily. Particles remain suspended in the air for many hours increasing the infective capabilities. In contrast, contamination of food and water is more difficult to undertake as large amounts of infective agents are required and dissemination using bombs or missiles would be of limited value because much of the infective agent is lost at impact or explosion. Contamination of mail items or direct injection can only be undertaken on a small scale and is unreliable. Finally, dissemination of infectious diseases could theoretically be undertaken by infiltrating a contagious person.

Nerve agents

Organophosphates

Organophosphates (see above) act as cholinesterase inhibitors to precipitate the rapid onset of cholinergic crisis by hyperstimulation of muscarinic and nicotinic receptors. Unless a specific reactivator (an oxime) is administered recovery will not occur for several months until acetylcholinesterases can be resynthesized. Organophosphates have been used in attacks in Japan and Iraq.

Sabin, tabun, soman, cyclosarin, VX

These nerve agents are all liquids at room temperature and are tasteless and odourless. However, most are spontaneously volatile and evaporate rapidly and spontaneously apart from VX, which is an oily liquid that evaporates more slowly. All are toxic via inhalation or skin absorption. The most likely agent to be used is sarin, which is usually absorbed by inhalation.

The onset of symptoms is with headache, pupillary constriction leading to blurred vision and cholinergic symptoms of rhinorrhoea, sialorrhoea and bronchorrhoea with secondary bronchoconstriction and respiratory distress. There may be nausea, vomiting, abdominal cramps and diarrhoea, bradyarrythmias and tachyarrhythmias and hypertensive crisis. Progressive cholinergic muscle involvement leads to fasciculation, weakness and respiratory muscle impairment causing apnoea and respiratory arrest. VX is a viscous liquid that degrades rapidly on exposure to the atmosphere but is easily absorbed through the skin and is extremely toxic causing rapid involvement of the NMJ leading to irreversible muscle contraction and a complete paralysis of all musculature. VR, a structural isomer of VX, also leads to cholinergic crisis with profound irreversible cholinergic weakness, seizures and cardiorespiratory arrest.

The management of nerve agents involves decontamination, supportive care and the administration of specific antidotes. Decontamination is undertaken by immediate removal of all clothing to prevent continuing exposure and careful scrubbing with water and antiseptic. Supportive care may require intubation and ventilatory support. Atropine is recommended as a first line treatment, this competes with acetylcholine at the postsynaptic muscarinic receptors and may prevent cholinergic crisis, thus drying secretions and resolving bronchoconstriction. It may be necessary to administer repeated doses of atropine every 5–10 minutes and extremely high doses may be required. Oximes (pralidoxime, obidoxime) cleave the nerve agent into harmless and rapidly metabolized fragments, thus restoring normal catalytic activity, they also react directly with acetylcholinesterases and therefore work equally at mixed cholinergic sites. Pralidoxime chloride is the drug of choice but its use is limited because binding leads to a chemical change in the nerve agent which blocks the ability of the oxime to reactivate the complexes. Prior to exposure pyridostigmine may be of value as it reversibly binds a proportion of acetylcholinesterase allowing it to become gradually available to counteract the effects of the permanent blockade caused by the nerve agent. This may be of use for rescue workers. The long-term effects of nerve agents remain unclear.

Other toxins and poisons

Antitoxin A

Antitoxin A is elaborated by a freshwater bacterium and is an acetylcholine agonist that causes cholinergic crisis with fixed permanent muscle contraction as it is not released from the receptor. Furthermore, the toxin inhibits acetylcholinesterase leading to a further cholinergic stimulation. A severe flaccid paralysis with respiratory muscle involvement leads to apnoea. Management is with supportive care as there is no specific antidote although oximes may have some value.

Mycotoxin

Mycotoxins are produced by fungi and may be used as biological agents as they are resistant to destruction and rapidly absorbed through the skin. The mechanism of action involves the blocking of protein synthesis leading to inhibition of mitochondrial metabolism. There may be rapid cutaneous, respiratory and CNS toxicity. Management requires decontamination and supportive care.

Ricin

Ricin is extracted from the bean of the castor plant. It inhibits DNA replication leading to cellular necrosis when internalized in cells. Historically, it has been used to assassinate individuals rather than as a weapon of mass destruction. It can be administered as an aerosol, droplet or by injection and leads to rapid tissue necrosis in the gastrointestinal tract, kidney and heart. Convulsions may occur. Management is supportive.

Marine toxins

Marine toxins are discussed above.

Dioxin and Agent Orange

These were particularly used during the Vietnam war as defoliants and herbicides. The long-term consequences are now recognized and there may be cognitive and neuropsychiatric impairment as well as a distal sensory peripheral neuropathy particularly affecting the lower limbs.

Biological botulism

Botulism has been discussed in Chapter 8. The toxin is highly potent and can be readily aerosolized and absorbed by inhalation or ingestion into the gastointestinal tract, persisting in this state for many weeks. The toxin is relatively easily degraded by exposure to heat, acidity or sunlight for >12 hours. Recovery follows only after there is regeneration of new axons which can take many months. Presynaptic inhibition of both cholinergic and autonomic (muscarinic) and motor (nicotinic) receptors leads to an extensive flaccid paralysis.

Anthrax

Spores of the Gram-positive organism *Bacillus anthracis* can be inhaled, ingested or absorbed through the skin and cause a severe haemorrhagic bacterial meningitis in addition to primarily pulmonary, cutaneous and gastrointestinal toxicity. The diagnosis is made difficult by the prolonged interval from exposure to presentation. Involvement of the CNS greatly increases the risk of mortality. Ciprofloxacin is the treatment of choice but doxycycline, clindamycin or rifampicin are also effective. Pre-exposure vaccination may have some protective effect. *B. anthracis* is easy to produce, the spores are hardy, highly infectious and remain in the environment for many years. They can be stored almost indefinitely and can only be removed by filtration with small pores or by formaldehyde. Aerosol deployment of dry spores risks secondary infection and spores could be effective in water or food supplies.

Smallpox

Smallpox is a potentially devastating infection caused by variola, which is a DNA virus, infectious in droplet form. The last known case was in 1977 but intact virus remains in a number of laboratories. The Variola virus invades mucosal cells of the respiratory system before viraemic dissemination to bone marrow, spleen and other lymph nodes. Immediate vaccination following exposure is essential and the subject should be isolated as soon as possible.

Other viruses

Arboviruses might be used as biological weapons because of high infectivity, low infectious dose and the absence of any specific treatment. However, most forms of arbovirus encephalitis are self-limiting. With supportive care patients recover well from these forms of infection although fatal encephalitis can occur. Vaccines are of limited benefit and treatment is with supportive care.

Tularemia

This is caused by *Francisella tularensis*, a non-motile aerobic Gram-positive coccobacillus that is highly infective and may cause a meningitis or encephalitis although an atypical pneumonia is more frequent. First line treatment is an aminoglycoside antibiotic (streptomycin or gentamycin); alternatives include doxycycline, chloramphenicol and ciprofloxacin.

Vitamin deficiencies and toxicity

Vitamin A

Vitamin A deficiency occurs in fat malabsorption syndromes and leads to a variety of ophthalmic disorders. Retinol is required for the synthesis of rhodopsin, a visual pigment necessary for normal rod function in the retina; its deficiency leads to night blindness. There may also be corneal ulceration and carotenization of the conjunctiva. 'Bitot spots' are white foam-like lesions, which appear on the side of the cornea and are characteristic of vitamin A deficiency.

Vitamin A toxicity is associated with ingestion of carotene-rich liver and proprietary treatments and may cause idiopathic intracranial hypertension. The skin is often dry and pruritic and generalized joint and bone pains occur. Serum retinol levels may be helpful to establish the diagnosis.

Vitamin B_1 (thiamine)

Thiamine is found in most food and cereals but reduced intestinal absorption occurs in alcoholism and malabsorption syndromes. Deficiency is also associated with malnutrition, inadequate parentral nutrition, haemodialysis, uraemia or repeated vomiting. Thiamine depeletion may develop acutely and is a medical emergency because of the development of congestive cardiac failure and peripheral oedema (wet beri-beri), a sensory axonal neuropathy (dry beri-beri) or Wernicke–Korsakoff syndrome (cerebral beri-beri). The effects of thiamine deficiency are discussed below.

Vitamin B_3 (niacin, nicotinic acid)

Niacin deficiency leads to the syndrome of pellagra. The condition occurs in populations that are dependent on corn but has decreased in frequency as white bread now is now enriched with niacin. Clinically pellagra is characterized by the development of dermatitis, diarrhoea and dementia (the three d's). The onset is usually with gastrointestinal symptoms including anorexia, diarrhoea and stomatitis. Skin changes are also frequently seen and erythema particularly affects the face, chest and dorsal surfaces of the hands and the feet. There may be mood changes, fatigue, malaise, lethargy and confusion with progression to neuropsychiatric disturbances including apathy, inattentiveness and memory loss or the development of spastic paraparesis with startle myoclonus. The cognitive impairment, which occurs in chronic alcoholics even with adequate thiamine replacement, is probably caused by niacin deficiency and is characterized by a defect in recent memory, visuospatial ability, abstract reasoning and speed of information processing. Treatment is with oral niacin replacement, often provided in food supplements.

Vitamin B_6 (pyridoxine)

This is important in the metabolism of many amino acids. Deficiency often occurs in infancy because of feeds containing inadequate levels of B_6. In children there may be hyperirritability, exaggerated auditory startle and recurrent convulsions leading to status epilepticus. In adults, pyridoxine deficiency is usually secondary to medication including isoniazid, hydralazine and penicillamine. There may be peripheral neuropathy with distal weakness and painful sensory loss, absent tendon reflexes and Romberg's sign. High dose pyridoxine also causes a distal sensory axonal neuropathy with sensory ataxia.

Vitamin B_{12} deficiency

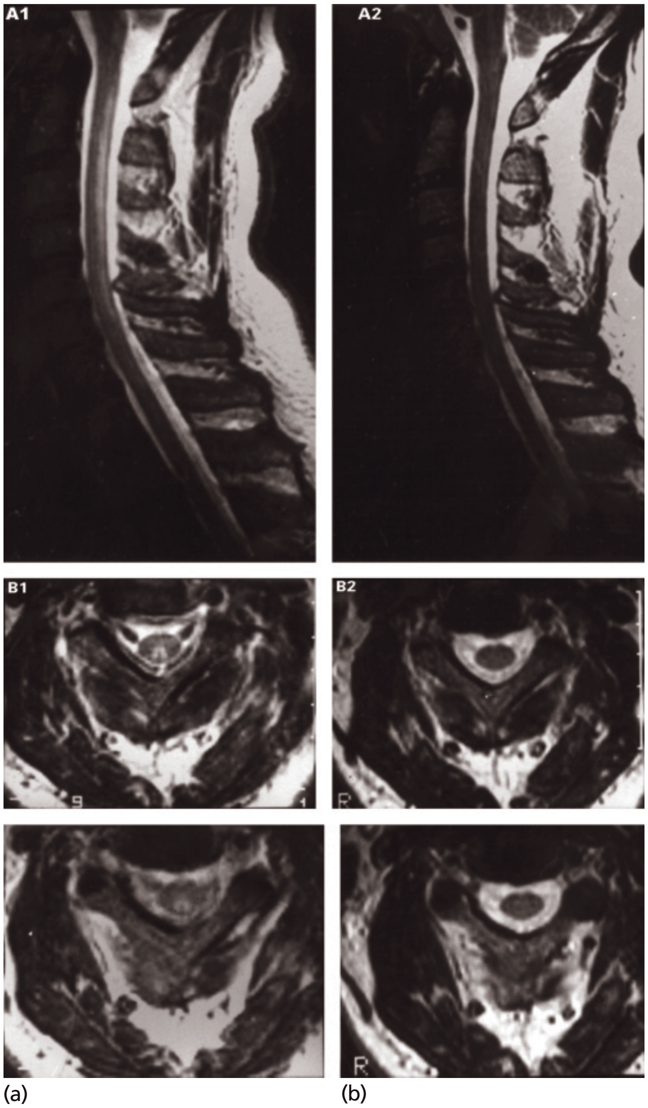
Vitamin B_{12} is abundant in meat, fish and animal by-products. Approximately 90% of total body B_{12} is stored in the liver. Because of the large body stores, even with severe impairment of B_{12} absorption, the symptoms and signs of B_{12} deficiency may take many years to evolve. Daily requirements are small and only rarely can B_{12} deficiency arise because of dietary insufficiency. It is associated with pernicious anaemia caused by defective intrinsic factor production by the gastric parietal cells but may also follow gastrectomy or small intestine disorder including surgical resection of the terminal ileum and blind loop syndrome. The elderly, vegetarians and patients taking H2 blockers for ulcers are at particularly high risk.

Systemic manifestations of vitamin B_{12} deficiency include gastrointestinal involvement, characterized by the development of glossitis and a pan-enteropathy with diarrhoea and malabsorption of nutrients. Neurological features occur in up to 40% of patients with B_{12} deficiency but these evolve over several months or longer. Symptoms develop insidiously with progressive paraesthesiae in the hands and feet with weakness and unsteadiness of gait culminating in peripheral neuropathy and myelopathy. Central manifestations include confusion, depression, progressive hallucination and mental slowing. Patients occasionally present with isolated cognitive or psychiatric disturbances and direct relationship between B_{12} and dementia remains unclear. There may also be optic neuropathy.

Subacute combined degeneration of the cord

This effect of B_{12} deficiency is characterized by a sensorimotor axonal neuropathy and myelopathy. Neuropathic manifestations include distal paraesthesiae, numbness, gait ataxia and diminished proprioception in the lower limbs, while the myelopathic component leads to variable motor impairment because of pyramidal tract dysfunction; the reflexes are variable depending on the extent of cord and peripheral nerve involvement with extensor plantar responses. Incontinence of bowel, bladder with impotence and postural hypotension occur as part of the myelopathy. Visual impairment is also associated with B_{12} deficiency with the development of optic atrophy, impaired acuity and centro-caecal scotoma. Brainstem cerebellar signs are occasionally present. Progressive cognitive impairment is characterized by memory loss, behavioural affective changes and occasionally stupor and coma. The blood film shows the development of a macrocytic anaemia with hypersegmented neutrophil nuclei and megaloblastic change in the bone marrow. Serum cobalamin levels may be used as a screening test and the Schilling test is valuable in demonstrating impaired absorption of vitamin B_{12} even if serum levels are normal. MRI scan may show extensive white matter change which can become confluent with disease progression culminating in leucoencephalopathy. The spinal cord shows abnormalities in the lateral and posterior columns with enhancement and residual changes may persist after treatment (Figure 18.4). Visual and somatosensory evoked potentials are delayed. Nerve conduction studies reveal small or absent sensory action potentials reflecting an axonal neuropathy in approximately 80% of patients.

The clinical features of nitrous oxide intoxication and the vacuolar myopathy of AIDS are identical to those of subacute combined degeneration. The pathological changes of subacute combined degeneration of the spinal cord include spongy change with focal loss of myelin and axonal destruction in the white matter of the spinal cord particularly affecting posterior and lateral columns of the cervical and upper thoracic spinal cord. The peripheral nerves show axonal degeneration without significant demyelination. There may also be involvement of the optic nerves and cerebral white matter.



(a) (b)

Figure 18.4 Subacute combined degeneration of the cord. On admission (a) and after initiation of cobalamin treatment (b). The hyper-intense lesions of the posterior column disappeared after treatment. (MRI T2W.) (From Hemmer *et al.* 1998, with permission.)

Treatment of B_{12} deficiency

With adequate treatment, some of the deficits of B_{12} deficiency may be reversible with most improvement occurring within the first 6 months of treatment. The myelopathy is least likely to make a complete recovery. B_{12} replacement should be given twice weekly for 2 weeks followed by monthly injections. If there is malabsorption of B_{12} then injections should be continued life-long. With full treatment at least partial improvement occurs in most patients but daily oral supplementation with large amounts of cobalamine may be necessary.

Folate deficiency

Absorption of folate takes place in the jejunum and ileum and levels are reduced in chronic alcoholism and following small bowel resection or disease. A number of drugs interfere with folate metabolism including sulfasalazine, methotrexate and azathioprine. Overt neurological deficit is unusual in folate deficiency but there may be mild cognitive impairment, depression and an increased risk of stroke or neural tube deficit in pregnancy. Folate deficiency may rarely produce a syndrome resembling subacute combined degeneration of B_{12} deficiency. Folate deficiency leads to elevated homocysteine levels, a risk factor for the development of cerebrovascular, cardiovascular and peripheral vascular disease. Folate is administered orally but may be given parenterally in acutely ill patients.

Vitamin D

Vitamin D deficiency is associated with hypoparathyroidism, hypophosphataemia, chronic renal failure, malabsorption, dietary deficiency or inadequate exposure to sunlight. Neurological presentation is as a proximal myopathy which may be associated with osteomalacia. There is proximal weakness with a characteristic waddling gait but no involvement of bulbar or ocular musculature. CK is elevated, electromyography (EMG) shows myopathic change and biopsy will confirm evidence of type II muscle fibre atrophy. Treatment is vitamin D replacement which leads to a slow recovery of the weakness.

Vitamin E

Vitamin E is fat-soluble and acts as a free radical scavenger and antioxidant. It is normally stored in large amounts so that clinical symptoms only become apparent after many years of deficiency, usually secondary to malabsorption in cystic fibrosis, adult coeliac disease or because of abnormalities of specific vitamin E receptors, e.g. abetalipoproteinaemia. There is progressive spinocerebellar degeneration with limb ataxia, because of involvement of the posterior columns, and an axonal, predominantly sensory, peripheral neuropathy with prominent involvement of proprioception. Rarely, pyramidal features may develop with extensor plantar responses and ocular signs including ptosis, nystagmus, external opthalmoplegia and optic neuritis. Investigation shows evidence of spiky red blood cells (acanthocytes) as well as retinal pigment change. Low serum vitamin E can be shown on assay but CSF is normal. Nerve conduction studies confirm a mild axonal neuropathy and occasionally the MRI scan shows high signal in the posterior columns. Treatment is with the recommended daily requirement of vitamin E of 10 mg/day. If the vitamin is deficient then the therapy should be given with the water-soluble tocopherol 200–600 mg/day.

Alcohol abuse

Alcohol abuse is extremely common and is associated with important cultural, economic and environmental factors; there is also a strong genetic component. It affects all socio-economic strata of society. Primary alcoholism may be defined as addiction to alcohol in the absence of an underlying cause. Physical dependence may become such a strong compulsion that psychopathology develops with neglect of self and family. This may culminate in severe disruption of general health, behaviour and cognitive function leading to loss of personal relationships and occupation. Secondary alcoholism occurs when excessive drinking is the consequence of other major psychiatric illness, e.g drug addiction, schizo-affective disorder or manic depression.

Metabolism of alcohol

Alcohol is rapidly absorbed from the gastrointestinal tract and is metabolized in the liver where it is oxidized to acetaldehyde by the action of alcohol dehydrogenase and other enzymes. The role of acetaldehyde in alcohol toxicity is uncertain but it is highly cytotoxic and is also readily metabolized to acetate by the mitochondrial enzyme acetaldehyde dehydrogenase. Tolerance to alcohol is the acquired resistance to its effects. Intoxication occurs because alcohol crosses the blood–brain barrier.

The clinical manifestations of alcohol may be divided into:

1 Effects of acute intoxication;
2 Effects of alcohol substitutes;
3 Withdrawal syndrome occurring after sudden abstinence; and
4 Chronic disorders associated with prolonged alcohol abuse.

Effects of acute intoxication

The effects of acute alcohol intoxication are widely accepted by many societies, particularly amongst young people. The initial behavioural effects of euphoria, social disinhibition, loss of restraint and reduced psychomotor capacity are well-recognized but progression to behaviour disturbance, irritability, slurred speech, ataxic gait, aggression and loss of control may have serious consequences with high levels of intoxication. Depressant effects including drowsiness, stupor and coma may supervene with the risk of vomiting, aspiration and respiratory impairment. Acute intoxication is associated with psychotic disturbances including an acute paranoid state with auditory hallucinations, anxiety, agitation, outbursts of aggression and inappropriate violent or even destructive social behaviour of which the patient may have no recollection. These periods of amnesia, in which there is no ability to retain short-term memories, increase in duration and persist into periods when sober and fully conscious. Symptoms occur with serum levels as low as 50–150 mg/dL (10–31 mmol/L) but in those with previous alcohol intake and induction of the hepatic enzymes, symptoms develop at a higher concentrations of blood alcohol. Extreme intoxication (>300 mg/dL or 65 mmol/L) results in cerebellar impairment (ataxic dysarthria and nystagmus) and coma associated with hypotension, respiratory depression and hypothermia, with death occurring from brainstem depression if the blood alcohol level exceeds 400 mg/100 mL. Because alcohol is rapidly absorbed acute intoxication may require sedation and treatment of agitation with haloperidol or chlorpromazine, or ventilatory support and haemodialysis, especially if there is a suggestion of methanol intake in addition.

Effects of alcohol substitutes

Methyl alcohol (methanol)

This is commonly used as a solvent and in antifreeze. It may be abused as a substitute for ethyl alcohol in 'meths'. It is directly toxic to the CNS as a depressant and is oxidized to formaldehyde and formic acid, which inhibit cytochrome oxidase and have a direct toxic effect on the putamen and optic nerves. Acute intoxication may be delayed for many hours. Delirium may develop at the onset but a rapid progression occurs to cause visual field loss, blindness secondary to retinal oedema, pseudobulbar palsy and cognitive impairment. Severe toxicity culminates in metabolic acidosis and cerebral oedema leading to respiratory failure, coma and death. In patients who recover from acute intoxication there may be residual blindness and parkinsonian features. Treatment involves reversing the acidosis with large doses of sodium bicarbonate, retarding the mechanism of methanol with ethyl alcohol or fomepizole and, where necessary, haemodialysis.

Ethylene glycol

This is also commonly used as a solvent, in antifreeze, air conditioners and fire extinguishers. It may contaminate proprietary alcoholic drinks or be ingested in suicide attempts. Intoxication is associated with lethargy and progressive hypersomnolence, hyperventilation with seizures and hypotension. There is a metabolic acidosis with an anion gap. Anuric renal failure develops which is also associated with seizures. With high levels there may be the delayed onset of a cranial neuropathy, which resolves slowly. Treatment is by haemodialysis with intravenous sodium bicarbonate and, if necessary, ethanol. Fomepizole (4-methylpyrazole) is also used as a competitive inhibitor of alcohol dehydrogenase.

Withdrawal syndromes

The severity of withdrawal symptoms is proportional to the level of previous alcohol intake and the abruptness of cessation. Withdrawal of alcohol in the chronic abuser may lead to the development of delirium tremens with CNS hyperexcitability, initially characterized by tremulousness with anxiety, insomnia, confusion, hyperactivity, hallucinations and seizures. The symptoms progressively worsen over several hours before settling, up to 72 hours after the last intake of alcohol. The tremor is generalized, present at rest and on action and may involve the face and tongue. It is associated with irritability and is usually present in the morning, but progressively worsens and increases in duration with prolonged withdrawal. There is usually an associated gastrointestinal disturbance with nausea, vomiting and autonomic hyperactivity with tachycardia, hypertension and sweating. Disturbing vivid auditory and visual hallucinations develop and these may persist for several days after the physical symptoms have settled. The patient frequently awakes lucid with no recollection of the acute delirious phase. Recurrence is common and, in severe cases, death may supervene. It is essential to consider the possibility of alcohol withdrawal in patients who develop confusion, tremor or seizures after being admitted to hospital for more than 12 hours. Severe withdrawal delirium tremens occurs in about 5% of patients withdrawing from alcohol and is associated with hyperpyrexia, ketoacidosis and circulatory collapse. Isolated hallucinations may occur in up to one-quarter of patients following withdrawal. They are often visual but occasionally auditory. Patients often lack insight into their hallucinations and their development indicates a poor prognosis with significant mortality.

Withdrawal seizures (rum fits)

These typically occur within the first 24–48 hours of withdrawal. They are generalized, tonic–clonic convulsive seizures, which usually occur singly or in brief clusters although status may develop. The EEG shows mild changes and generally reverts to normality within a few days. Even if status develops, the condition is usually self-limiting and patients often do not require antiepileptic medication although acute treatment with lorazepam or diazepam may be necessary.

Management of alcohol withdrawal

Minor symptoms can be managed with simple reassurance and nursing in a calm quiet well-lit environment although benzodiazepines may be helpful. Moderate symptoms, including autonomic hyperactivity and irritability, necessitate an incremental dose of benzodiazepines. Severe symptoms associated with confusion, poor cooperation, restlessness and aggressive behaviour may require intravenous Diazemuls given by slow injection and, if further treatment is necessary, haloperidol 5–10 mg i.m. or 5 mg twice daily up to 20 mg/day is the treatment of choice. Chlordiazepoxide, clomethiazole or clonidine are also effective.

Chronic disorders associated with prolonged alcohol abuse

Wernicke–Korsakoff syndrome

This is a complex of symptoms and signs resulting from an acquired nutritional deficiency of thiamine (vitamin B_1) rather than any direct toxic effect of alcohol. Thiamine (and other B vitamins) is a co-enzyme in glucose and lipid metabolism, amino acid production and neurotransmitter synthesis. Because thiamine stores are relatively small and there is a large daily turnover, deficiency may occur within 2–3 weeks of low intake. The brain is particularly sensitive to disturbance of complex B vitamin-dependent metabolism of glucose.

Wernicke's encephalopathy may present as an acute or slowly evolving disorder, often precipitated by an intercurrent medical event or metabolic stress such as trauma or infection. In addition to alcohol, it is caused by other conditions in which a depletion of thiamine may occur: hyperemesis of pregnancy, systemic malignancy, haemo- or peritoneal dialysis, gastrointestinal surgery, prolonged intravenous feeding, anorexia and AIDS. The acute syndrome is characterized by apathy, confusion, impairment of ocular motility and cerebellar ataxia lapsing into an encephalopathy with progressive disturbance of behaviour, personality, orientation and cognitive function developing over days or weeks leading to stupor, coma and ultimately death. There may be hallucinations, perceptual disorder and agitation. Ocular signs are characteristic and include ophthalmoplegia, nystagmus and conjugate gaze palsy. The ophthalmoplegia is initially caused by paresis of the lateral recti with subsequent involvement of other ocular muscles leading to total ophthalmoplegia. Nystagmus may be both horizontal and vertical and there is also sluggish pupillary response to light with light-near dissociation. Fundal examination shows small retinal haemorrhages and occasionally optic neuropathy develops. Progressive truncal and gait ataxia is common but the limbs are rarely involved.

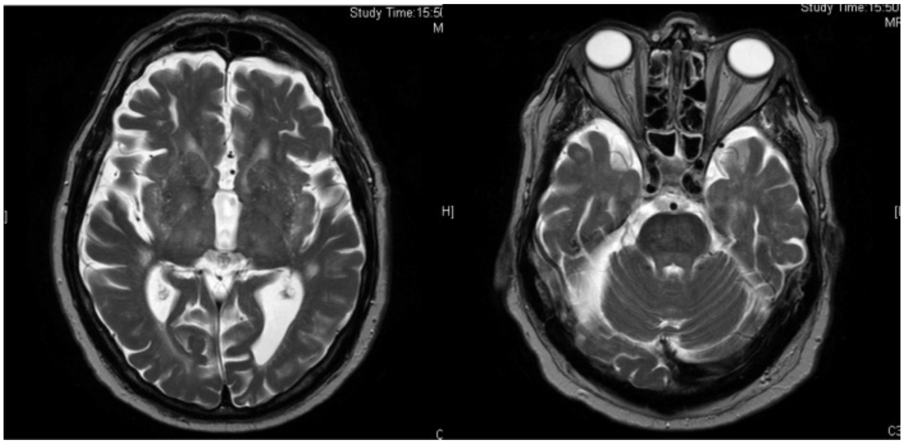


Figure 18.5 Wernicke's syndrome. T2-weighted MRI showing high intensity lesions in the medial thalami and peri-aqueductal grey matter of the midbrain.

MRI shows high T2 signal in the peri-aqueductal and the paraventricular region of the medial thalamus and hypothalamus while the mamillary bodies appear shrunken (Figure 18.5). CSF is characterized by elevated protein, serum thiamine; erythrocyte transketolase activity is reduced. The pathology in Wernicke's syndrome shows symmetrical haemorrhagic and necrotic change predominantly affecting the mamillary bodies, dorsal medial nucleus of the thalamus and peri-aqueductal region as well as the tegmentum of the pons. Treatment is by thiamine given immediately commencing at 50–100 mg parenterally in the acute stages. Untreated Wernicke's encephalopathy is associated with a significant mortality but with adequate treatment the signs resolve rapidly.

Korsakoff's syndrome

This is a progressive and severe amnestic syndrome which is incompletely reversible. Memory is preferentially involved in comparison to other cognitive function with a profound impairment of both retrograde and antegrade memory. The memory of recent past is usually more severely affected than distant past while language and calculation abilities are well preserved. There may also be perceptual difficulties and loss of insight although this is often less marked. Patients show striking loss of working memory with disorientation in person and place but retain reference memory, alertness, attention, calculation and, at onset, normal social behaviour. The condition is characterized by confabulation, the deliberate attempt to hide the memory defect by fabricating events.

Pathologically, the memory impairment of Korsakoff's syndrome is associated with selective necrosis of the basal septal nuclei of the frontal lobes, the temporal lobes and diencephalon. In alcoholism Korsakoff's syndrome is caused by thiamine deficiency but it may also occur following infarction, anoxia, trauma, tumours involving the frontotemporal regions, temporal lobe epilepsy and herpes simplex encephalitis (Figure 18.6; Plate 18.5).

Treatment requires urgent and high doses of thiamine replacement and should be continued until a noticeable improvement has occurred and for as long as clinical improvement continues. Improvement in memory function is slow and usually incomplete. Up to one-quarter of patients show no recovery while only slight improvement occurs in the remaining patients. Significant or complete recovery is rare.

Wernicke–Korsakoff syndrome may be difficult to detect and a high index of suspicion is necessary in all patients who abuse alcohol and those with poor diet or gastrointestinal disturbance including diarrhoea and vomiting.

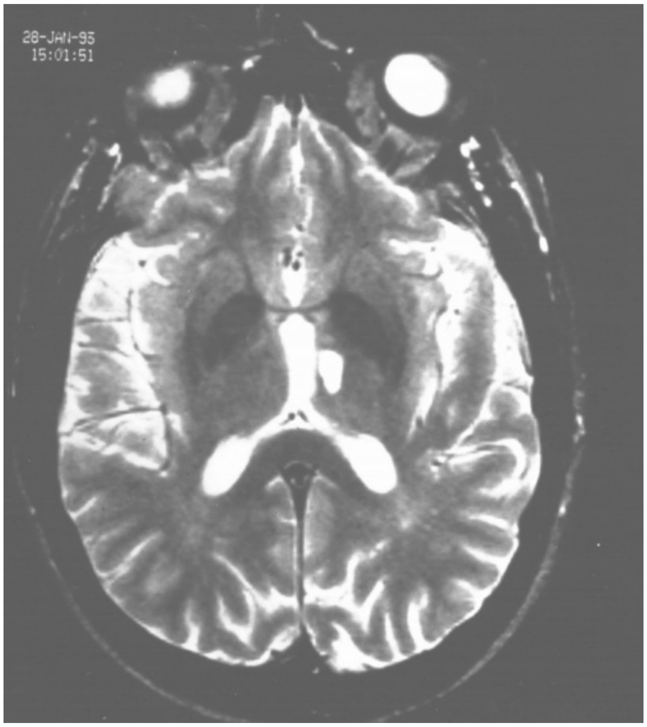


Figure 18.6 Korsakoff's syndrome. T2-weighted axial MRI showing thalamic infarction. (Courtesy of Professor M. Kopelman, St. Thomas' Hospital.)

Cerebellar ataxia

Chronic alcohol abuse is the most common cause of acquired cerebellar atrophy and is often associated with alcohol polyneuropathy. The ataxia usually affects men and may be so severe that the patient is unable to stand without support. Patients walk with a broad-based gait with slow short steps but limb ataxia and speech disturbance are minimal although cerebellar abnormalities of ocular movement are often present. Progressive unsteadiness evolves over several months with truncal ataxia and mild gait disturbance. Abstinence from alcohol leads to a slow and incomplete improvement. Pathological examination shows selective atrophy of the anterior and superior part of the cerebellar vermis with cell loss particularly involving the Purkinje cells. Cerebellar ataxia may be associated with Wernicke's encephalopathy or occur in isolation.

Confusional state and dementia

Cortical atrophy and ventricular dilatation occur with prolonged alcohol intake. This is associated with a global confusion characterized by progressive indifference to surroundings and abulia may occur. Patients are easily aroused but are disorientated with cognitive deficits which may worsen and become fixed, interfering with activities of daily living, before evolving into frank dementia which may persist even after discontinuation of alcohol.

Alcoholic peripheral neuropathy

Sensorimotor axonal peripheral neuropathy is a characteristic feature of alcohol abuse, occurring as a consequence of thiamine deficiency in Wernicke's encephalopathy or because of direct alcohol toxicity. The neuropathy is usually insidious in onset, often mild and predominantly sensory. However, rapid progression may occur with motor impairment severe enough to affect gait. Painful symmetrical sensory loss occurs to all modalities, particularly affecting the lower limbs; it is characterized by distal tingling, burning and lancinating pain. Autonomic involvement is manifest as impotence, sweating, pupillary abnormalities and postural hypotension. Investigation shows a macrocytosis and elevation of hepatic enzymes. There may be an elevated CSF protein and nerve conduction studies show an axonal polyneuropathy predominantly affecting sensory and motor action potential with slowing of conduction velocity. Management is discontinuation of alcohol consumption and ensuring adequate nutritional intake with thiamine and vitamin B supplements.

Alcoholic myopathy

Acute myopathy can occur with chronic alcohol abuse but may also follow binge intake. It is secondary to the direct toxic effects of alcohol although other factors including muscle crush, seizures and electrolyte disturbances may contribute. The onset is with acute and severe muscle pain, cramp, swelling and a rise in the CK, evolving rapidly into focal or generalized myopathic weakness often with selective involvement of the calves. A cardiomyopathy may coexist. Although recovery usually occurs within days or weeks, rhabdomyolysis and myoglobunuria may occur, leading to hyperkalaemia and renal failure. A more chronic myopathy is associated with prolonged consistent alcohol abuse, characterized by slowly developing, painful proximal myopathy particularly affecting the shoulder and hip girdle muscles. This myopathy may be asymptomatic and noted because of an isolated elevation in CK. EMG shows myopathic features and there may also be a coexisting neuropathy. Biopsy of chronic alcohol myopathy shows no significant muscle fibre necrosis but atrophy affecting type II (especially type IIB) fibres. In the acute form there is scattered muscle fibre necrosis with regeneration. The myopathy may be reversible with many months of abstinence and good nutrition.

Other neurological complications of alcohol abuse

Marchiafava–Bignami syndrome

This is a condition associated with strong red wine, usually chianti, that affects severe and chronic alcoholics in middle or late life. The aetiology is unknown and presentation is variable with a slowly progressive disturbance of cognitive function, personality and behaviour. There is progressive motor slowing with incontinence, frontal release signs and a broad-based gait. There may be cognitive impairment, dysarthria, hemiparesis, apraxia, aphasia and seizures and occasionally a patient may present in stupor or coma. There is selective demyelination of the central portion of the corpus callosum with sparing of the anterior and posterior portions, other white matter tracts are also affected. Treatment is with nutritional support and rehabilitation but recovery is variable. Imaging shows high signal lesions on T2 MRI in the corpus callosum and anterior commissure.

Fetal alcohol syndrome

Prenatal exposure to ethanol impairs fetal growth and neurodevelopment. There may be dysmorphic facial features and microcephaly, mental retardation and learning difficulties including speech delay and hyperactivity.

Psychiatric sequelae

In chronic alcohol abuse depressive illness is common, particularly on withdrawal, and up to one-quarter of patients fulfil the criteria for a major depressive disorder; however, it often remits after several months and rarely requires antidepressant medication. Some patients also have an anxiety disorder which may develop into frank psychotic symptoms during withdrawal.

Traumatic injury

Traumatic injuries to the head may occur during intoxication causing parenchymal contusions, subdural or extradural haematoma, subarachnoid haemorrhage and lead to post-traumatic epilepsy.

Compressive neuropathies

The most common neuropathies occurring in alcohol abuse include compression of the radial nerve at the spiral groove causing 'Saturday night palsy'. The peroneal nerve may be trapped at the fibula head leading to a foot drop and the sciatic nerve may be compressed in the gluteal region.

Amblyopia

Amblyopia occurs as a consequence of chronic alcoholism and is associated with poor dietary and heavy tobacco intake and weight loss. Progressive optic nerve involvement leads to painless visual loss affecting both eyes with diminished visual acuity with centro-caecal scotoma and mild disc pallor. The treatment is with adequate diet and B vitamins which generally leads to visual recovery.

Alcoholic cirrhosis

It must be emphasized that neurological effects of alcohol abuse run in parallel with systemic factors. Alcohol-related cirrhosis is the most common and serious manifestation. Patients may develop porto-systemic encephalopathy, tremor, myoclonus and asterixis.

Strachan's syndrome

This is a severe painful ataxic sensorimotor neuropathy associated with visual loss resulting from amblyopia, tinnitus, gastritis and stomatitis. The condition is related to nutritional deficits. There have been outbreaks of the condition in Cuba associated with retrobulbar optic neuropathy, peripheral neuropathy, sensory neural hearing loss and myelopathy with spastic paraparesis and dysphonia. The aetiology remains unclear but a relationship to poor nutrition and heavy alcohol and tobacco exposure has been noted.

Other deficiency states associated with neurological manifestations

Copper deficiency

This occurs following gastrointestinal disturbance, in particular after gastrectomy. Copper is essential to the nervous system and bone marrow and functions as a prosthetic group in key enzymes involved in catecholamine synthesis, the respiratory chain, folate metabolism and antioxidant function. The most common neurological manifestation of acquired copper deficiency is a myeloneuropathy with sensory ataxia. The MRI shows increased T2 signal in the dorsal spinal cord. The condition appears clinically and radiologically identical to subacute combined degeneration of the cord associated with B_{12} deficiency.

Magnesium deficiency

This may also occur after gastrointestinal surgery or with chronic use of diuretics. It is an essential co-enzyme involved in the metabolism of thiamine and its deficiency may lead to an impaired response to thiamine in Wernicke's encephalopathy resulting from alcohol or hyperemesis gravidum.

Drugs of abuse

Epidemiology

The clinical assessment of drug abuse is extremely difficult because addicts may use several drugs at one time, or abuse alcohol concurrently. Furthermore, the drug may be contaminated either at source or at the time of administration and the metabolism of drugs of abuse is unpredictable depending on dosage, mode of administration and the ability of the body to metabolize the drug.

Drug dependence is both psychological when drug use is compulsive because of pleasurable or dysphoric effects and physical if discontinuation of the drug will lead to serious and painful symptoms. Drug users develop tolerance and require larger doses to maintain the effects of the drug and to prevent the development of withdrawal symptoms.

There are five major groups of drugs of abuse:

1 Stimulants;
2 Sedatives;
3 Hallucinogens;
4 Organic solvents; and
5 Drugs used to enhance athletic performance.

Stimulants

Stimulants (Table 18.4) share the ability to enhance transmission at the catecholaminergic synapse and therefore have common pharmacological and toxic effects and also develop cross-tolerance. Stimulants are abused because they cause elation, increased alertness and motor activity as a consequence of their central effects. Prolonged excessive use is associated with motor manifestations including tics, tremor, myoclonus and an acute dystonic reaction.

Amphetamines

Dexamphetamine, the dextro-isomer of amphetamine, is used in clinical practice. Metamphetamine ('crystal meths' or 'ice') is widely abused. Acute intoxication is characterized by increased alertness, a sense of self-confidence and well-being, euphoria and extrovert behaviour, loss of appetitie and the desire to sleep, tremor, dilated pupils, tachycardia and hypertension. In extreme cases there may be paranoid delusions, hallucinations and violence. Prolonged intoxication may lead to convulsions,

Table 18.4 Stimulants commonly used as drugs of abuse.

Cocaine/crack
Amphetamines
3,4-Methylene dioxymethyl amphetamine (MDMA, Ecstasy)
Ephedrine
Phenylpropanolamine methylphenidate
Khat

hyperthermia, rhabdomyolysis and intracerebral haemorrhage. Stroke resulting from stimulant abuse is discussed below.

Designer drugs

Designer drugs are synthetic derivatives, usually amphetamine analogues. Ecstasy (MDMA) is a derivative of methamphetamine that is widely used as a stimulant, euphoric and hallucinogen. In high doses it has an amphetamine-like stimulant effect and unpredictable toxicity, exacerbated by dehydration. It may cause an acute toxic reaction with headache, hypertension, hyperpyrexia, seizures, rhabdomyolysis and the development of a hypertonic state with hepatic failure, coagulopathy, coma and death. Cerebral infarction or haemorrhage is rare. MDMA causes a massive central serotoninergic discharge which accounts for its psychic effects. There may be permanent impairment of memory. Several other amphetamine-derived drugs are widely used; all have similar effects following acute and prolonged intoxication.

Methylphenidate (Ritalin)

This can rarely cause an amphetamine-like syndrome with central disturbance seizures and intracerebral haemorrhage.

Khat

Khat is a flowering plant native to East Africa and the Arabian Peninsula. The leaves contain the alkaloid cathinone, an amphetamine-like stimulant. The leaves have been chewed for many years as a recreational drug within the region where it naturally grows because only fresh leaves are strongly psycho-active. Its stimulatory effects include a feeling of euphoria, excitement, increased alertness and sexual arousal. Toxic effects include anorexia, tremor, tachycardia, arrhythmia, hypotension and respiratory arrest. Improved air transport has led to extensive smuggling of the drug with a global distribution. Cathinone breaks down to cathine and norephedrine. This occurs after khat has been ingested or if the leaves are left to dry for more than 48 hours.

Methcathinone (‘cat’) is a derivative of cathinone. It is inexpensively and easily manufactured as a designer drug from its precursor ephedrine. It has a similar amphetamine-like stimulant effect when snorted, ingested or injected.

MPTP

Methylphenyltetrahydropyridine (MPTP) was developed in the USA as a designer drug with close clinical similarities to amphetamine. The effects of abuse were similar but some abusers developed a moderate to severe parkinsonian syndrome with bradykinesis, freezing, rigidity, instability, dysarthria and a symmetrical parkinsonian tremor. There was a variable response to levodopa with the development of typical motor fluctuations and dyskinesiae. Pathological features include moderate to severe neuronal loss and gliosis in the substantia nigra without Lewy bodies.

Cocaine

Cocaine is the most commonly abused psychomotor stimulant and is administered intranasally, parenterally or smoked as crack. Moderate doses are associated with mood elevation, increased alertness, reduced fatigue and enhanced performance but psychiatric effects develop rapidly including paranoia, delusions, hallucinations, choreo-athetoid movements and agitation. Chronic abuse may lead to progressive neuropsychiatric features including restlessness, irritability and psychotic aggressive paranoid states. These are associated with visual and auditory hallucinations with amphetamine abuse and violent behaviour with the cocaine alkaloid, crack. Long-term abuse of stimulants may lead to toxic encephalopathy or a fixed cognitive dysfunction with cerebral atrophy.

Conditions caused by stimulant abuse

Stroke

This may occur as a consequence of stimulant abuse for several reasons. It is associated with vasoconstriction, dissection and vasculitis occurring with amphetamine and cocaine. Furthermore, cardiac thrombus may embolize to the brain in patients with infective endocarditis or cardiomyopathy caused by arrhythmias or because foreign body material may be injected with the drug. Stroke may also be a consequence of endocarditis causing mycotic aneurysms or haemorrhagic transformation in cerebral infarction. Crack cocaine is the most important cause of drug-related stroke accounting for about 50% of all cases and being much more common than amphetamine-related stroke.

Haemorrhagic stroke

This is particularly associated with cocaine and seems to occur with intranasal or intravenous usage or smoking crack. Intracerebral haemorrhage is usually in basal ganglia but is occasionally lobar, intraventricular or subarachnoid. A pre-existing aneurysm or arteriovenous malformation may rupture.

Cerebral infarction

This is also associated with smoking crack cocaine. Infarction often affects the cortical or deep penetrating arteries, but anterior spinal artery occlusion also occurs. The onset of stroke following use of amphetamine or crack cocaine is rapid because of blood pressure surges. Approximately 50% occur in the middle cerebral artery territory. Imaging shows asymptomatic subcortical white matter lesions are common in crack and cocaine users.

Vasculitis

This is seen more commonly with amphetamine than cocaine. It usually evolves rapidly with headache, progressive encephalopathy and raised ESR. Diffuse vasospasm is associated with bleeding or focal narrowing; there may also be a vasculitis involving small calibre vessels and necrosis. Treatment is with high dose steroids.

Other effects of stimulant abuse

In addition to stroke and epilepsy, systemic complications of stimulants include the development of hyperthermia, dehydration and rhabdomyolysis with an increased risk of myocardial infarction and cardiac arrhythmia. Cocaine and amphetamine may also give rise to movement disorders including vocal and motor tics, chorea, dystonia and acute dystonic reaction of the head and neck. There may also be an oromandibular dyskinesia. Treatment is supportive with attempts to cool the patient, reduce blood pressure and maintain oxygenation. Neuroleptics, anxiolytics and sedatives may be necessary and seizures should be treated appropriately. Withdrawal of cocaine can be difficult as the tolerance develops to the euphoric and anorexic effects of the drug and the psychiatric manifestations may worsen.

Sedatives

Opiates

Heroin and morphine are highly addictive drugs which are usually administered intravenously but can be sniffed, smoked or injected subcutaneously (skin popping). Intravenous administration is often non-sterile and may lead to infective complications (Table 18.5).

The effects of heroin are the same as morphine but more powerful. There is an initial analgesic effect and then a sense of 'rush' with euphoria or dysphoria before drowsiness and hallucinations. Systemic features include pruritus, dry mouth, nausea, vomiting, constipation and urinary retention. There may be severe pupillary constriction before the development of respiratory depression, cerebral anoxia and post-anoxic encephalopathy. The immediate effects can be reversed with naloxone, a safe and effective antidote which should be given to anyone with a suspected opiate overdose. If the patient has not been discovered for a prolonged period of time there may be extensive compression and stretching of peripheral nerves and damage to the brachial plexus, common peroneal, ulnar or sciatic nerves with secondary ischaemia. Rhabdomyolysis may be caused by a compartment syndrome as a consequence of trauma, hypotension, fever and seizures or brought about by direct opiate toxicity. It occurs after prolonged periods of unconsciousness and may lead to myoglobinuria and renal failure. Repeated intramuscular injections can also lead to focal fibrosis and weakness in injected muscles with contractures. Stroke may occur secondary to an infective arteritis or to the development of mycotic aneurysms but infarction may also be a consequence of paradoxical embolism or contaminants. An acute myelopathy may occur with excessive heroin abuse with paraparesis, urinary retention and segmental sensory level, and urinary retention. A distal sensory or sensorimotor neuropathy may also occur. Inhalation of heroin pyrolate, particularly if contaminated by heating the drug on aluminium foil, may cause toxic encephalopathy with extensive white matter change on MRI (Figure 18.7).

Table 18.5 Infective complications of non-sterile intravenous drug administration.

Local abscess	Infectious hepatitis
Cellulitis	Liver abscess
Infective endocarditis	Cerebral abscess
Botulism	Septic arthritis
Tetanus	Mycotic aneurysms
Embolic infarction	Osteomyelitis
Meningitis	Discitis
Pyogenic arthritis	HIV
	Septicaemia

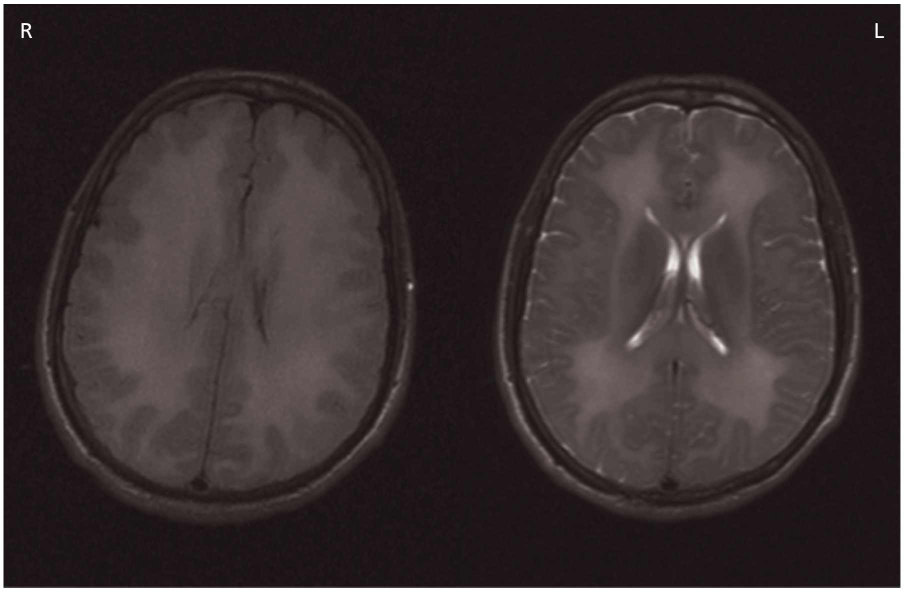


Figure 18.7 Toxic encephalopathy caused by inhalation of heroin pyrolate. MRI T2W scan showing extensive white matter change.

The symptoms and signs of withdrawal from opioids may appear within hours and include the characteristic syndrome of drug craving, restlessness and irritability, followed by the development of autonomic flu-like symptoms, sweating, lacrimation and rhinorrhoea. There may be piloerection, abdominal cramps, diarrhoea and coughing. The symptoms may develop rapidly following administration of naloxone but controlled withdrawal ought not to be dangerous and treatment of symptoms with oral methadone, a long-acting opiate, may ameliorate the symptoms. Clonidine and α_2-adrenergic agonists suppress the autonomic disturbances of opioid withdrawal.

Barbiturates

Barbiturates are abused because of their euphoric and sedative actions which are similar to alcohol. Acute intoxication leads to slurred speech, gait ataxia, coma, hypotension and eventually respiratory depression with apnoea. Treatment is supportive and involves the use of gastric lavage. When barbiturates are withdrawn acutely there may be irritability, tremor, tachycardia and a reduced seizure threshold; it may be necessary to reinstitute the barbiturate before reducing with gradual tapering dosage.

Benzodiazepines

Benzodiazepines, when used acutely, induce a comfortable sensation of lassitude, but in excessive doses there is progressive drowsiness, confusion, euphoria and impairment of psychomotor function leading to stupor and coma. The effects of acute overdoses can be reversed by flumazenil which is a specific antagonist, but this is short-lived. Chronic use of benzodiazepines leads to tolerance and physical dependence. Withdrawal symptoms develop within 24 hours of cessation of the use of short-acting benzodiazepines leading to irritability, increased sensitivity to light and sound and autonomic disturbance including tremor and tachycardia which may develop into delirium and hallucinosis; seizures may be provoked.

Hallucinogens

Hallucinogens are abused because of the heightened sensory perception with eventual hallucinogenic effects (Table 18.6). The subject experiences perceptual change, decreased pain sensation and autonomic effects which may include flushing, sweating, hypertension and tachycardia. Abuse is associated with an acute confusional state, ataxia, dysarthria and nystagmus. Numbness and perceptual change develop with features of self-mutilation, convulsions, dystonia and coma.

Table 18.6 Hallucinogens commonly used as drugs of abuse.

Phencyclidine
Lysergic acid diethylamide (LSD)
Ketamine
Marijuana
GABA hydroxybutyrate (GHB)
Solvents
Psilocybin (magic mushrooms)

Phencyclidine (angel dust)

This is taken orally, nasally or by inhalation and has a mixture of effects including a euphoric or dysphoric state, which may lead to catatonia and psychosis with chronic abuse.

Lysergic acid diethylamide (LSD)

This is a hallucinogen that alters perception, mood and thought. Acute effects are associated with dizziness, blurred vision, nausea and weakness. There is often euphoria, depersonalization, distortion of time and bizarre behavioural effects, including arousal and depression, which may lead to accidents or suicide. Chronic abuse has been associated with cerebral infarction and cognitive deficits.

Marijuana

Marijuana can be smoked, eaten or taken intravenously. It is widely abused because of its effects on memory, mood, judgement and sense of time. It induces a sense of relaxation with a subjective slowing of time with euphoria and depersonalization. In high doses there may be a toxic psychosis with hallucination, paranoia and a variable degree of anxiety, aggressiveness or sedation and sleepiness. The long-term consequences of abuse remain uncertain but paranoia and panic reaction may occur. Tolerance leads to a degree of irritability, restlessness and insomnia.

Ketamine

Ketamine is primarily used as an anaesthetic but has hallucinogenic properties. It is a drug of abuse and in large doses may lead to coma in humans while moderate doses can cause euphoria, relaxation and paranoia. Prolonged use leads to a long-term syndrome of psychosis, agitation, bizarre behaviour and catatonia.

GABA hydroxybutyrate

GABA hydroxybutyrate (GHB) induces euphoria, disinhibition and loss of short-term memory but its use is associated with sedation, disorientation and vomiting. In higher doses, seizures may develop.

Anticholinergics

These may also be used as recreational drugs because they can cause hallucinations and delirium. Excessive anticholinergic stimulation is associated with mydriasis, dry flushed skin, tachycardia, urinary retention and fever. In severe overdoses there may be myoclonus, seizures, coma and death.

Solvents

Lighter fluids, varnishes and paint thinners are frequently abused as inhalants because they are based on organic solvents including toluene, hexane and benzene. Their use is associated with a characteristic rash with inflammation around the mouth and the nose. Inhalation of low doses leads to a feeling of exhilaration, light-headedness and giddiness with auditory and visual hallucinations. With more prolonged or severe usage there may be vomiting, tinnitus, headache and eventually the development of seizures. Long-term exposure causes toxic encephalopathy with progressive impairment of coordination, cognition and the development of diplopia and ataxia with increasing disorientation, confusion, respiratory depression and coma. Toluene particularly can give rise to dementia, ataxia, oculomotor and brainstem dysfunction, and pyramidal features. Long-term complications include cardiac arrhythmias, suffocation from the use of plastic bags during inhalation, vomiting, aspiration and peripheral neuropathy. Sudden death can occur. MRI may show widespread white matter abnormalities.

Athletic performance-enhancing drugs

The neurotoxicity of some of these drugs is uncertain. Anabolic steroids including corticosteroids, insulin and growth hormone have direct physiological effect in building muscle. Stimulants, including amphetamine and cocaine, are also used to heighten alertness, reduce fatigue and prolong endurance. Erythropoietin (EPO) increases haemoglobin and oxygen delivery in endurance sports and β_2-agonists have a fat burning effect. Control of these drugs is variable and their effects may be unpredictable.

Investigation of suspected substance abuse

The first line of investigation is a urine toxicology screen, which may become positive within hours of ingestion. The toxicology screen remains positive for variable periods depending on the drug used and the presence of coincidental alcohol use. Positivity for amphetamine, cocaine, barbiturates and morphine is relatively short but benzodiazepines and heroin remain detectable for up to 8 weeks.

Imaging and angiography may show the presence of abscesses, an incidental arteriovenous malformation, aneurysm or mycotic aneurysm. Serology for syphilis and HIV is necessary and an echocardiogram is undertaken to exclude endocarditis. CSF examination may indicate infective CNS. Ultimately, cerebral and meningeal biopsy may be indicated.

Adverse reactions to drugs

Adverse reactions to drugs are a common cause of neurological morbidity and mortality. Drug reactions commonly lead to a variety of manifestations which may mimic naturally occurring neurological disease. There are many individual anecdotal case reports suggesting drugs are relevant to the aetiology of individual conditions but a clear causal relationship is much more difficult to establish. Throughout this section only the most important or most common forms of neurological drug toxicity are discussed.

Seizures

Many drugs induce seizures in healthy individuals or, more commonly, provoke seizures in patients with pre-existing epilepsy or a low seizure threshold (Table 18.7). Iatrogenic seizures may also occur as a consequence of withdrawal of antiepileptic medication or be provoked by other medical procedures such as surgery, electroconvulsive therapy, labour and delivery or intrathecal chemotherapy. Other predisposing factors include metabolic abnormalities, organ failure, water intoxication or electrolyte abnormalities, particularly hyponatraemia.

Headache

Headache may occur either as a direct consequence of medication or because the medication has acted as a trigger in a predisposed individual (Table 18.8). Acute exposure may cause a primary headache often brought about by vasodilatation. The most common drugs causing headaches are non-steroidal anti-inflammatory drugs (indometacin, diclofenac), nifedipine, cimetidine, ranitidine, β-blockers (atenolol, metoprolol, propranolol) and vasodilatator drugs (including glyceryltrinitrate). A number of drugs also cause or exacerbate a tendency to migraine including cimetidine, the oral contraceptive pill, atenolol, indomethacin and nifedipine. Chronic headache is associated with the overuse of medication or

Table 18.7 Drugs that may provoke seizures.

Respiratory agents – theophylline, aminophylline, terbutaline
Psychotropic medication – phenothiazines, clozapine, butyrophenones, lithium
Antimicrobial agents – antibiotics (isoniazid, nalidixic acid), antifungal, antituberculous, antihelminthics
CNS stimulants – caffeine, cocaine, amphetamines, methylphenidate
Antineoplastic agents
Opiates and narcotic agents – pethidine, morphine
Vaccines
Radiological contrast agents
Local anaesthetics, e.g. lidocaine

Table 18.8 Drugs that may cause headache.

Non-steroidal anti-inflammatory drugs	Ibuprofen, diclofenac, celecoxib
Analgesics	Overuse
Antimicrobial medication	Sulphonamides, cephalosporins, ciprofloxacin, isoniazid, penicillin
Antiviral agents	Valaciclovir
Cytotoxic medication	Cytosine arabinoside
Corticosteroids	
Carbamazepine	
Intravenous immunoglobulin	
Intrathecal injection	Cytotoxics e.g. methotrexate and contrast
Others	Antimicrobials, baclofen, spinal anaesthesia

by drug withdrawal. Headaches resulting from transient hypertension occur with monoamine oxidase inhibitors (MAOIs), as a reaction to treatment or when sympathomimetic agents are given concurrently. Intravenous immunoglobulin (IVIG) commonly gives rise to headache particularly in known migraine sufferers. Idiopathic intracranial hypertension occurs predominantly in young women who are overweight and is particularly associated with use of the oral contraceptive drug, vitamin A intoxication or a variety of other medications including antibiotics (tetracycline, ampicillin, nitrofurantoin), non-steroidal anti-inflammatory drugs (naproxen, ibuprofen), retinoids, danazole, amiodarone, perhexiline and thyroxine.

Headache may also occur as a consequence of drug-induced aseptic meningitis (e.g. NSAIDs).

Confusional states

Drugs are a common cause of a confusional state, manifest as a fluctuating level of consciousness, diminished awareness, impairment of intention and memory, disorientation, hallucination and paranoid delusions. The primary drugs that may be responsible are summarized in Table 18.9.

Table 18.9 Drugs associated with confusional states.

Tranquillizers and hypnotics – barbiturates, benzodiazepines
Antiparkinsonian medication
Antidepressants including SSRIs
Abrupt withdrawal of drugs

SSRI, selective serotonin re-uptake inhibitor.

Encephalopathy

Clouding of consciousness or delirium is commonly caused by multiple general medical factors but is particularly related to the effects of medication. It may be manifest as a disturbance of consciousness but there may also be changes in cognition or perception. The disturbances develop over a relatively short period of time and fluctuate during the course of the day. A large number of drugs may cause delirium but most reports are anecdotal. The most important medications may have multiple effects (Table 18.10).

Memory disturbance

Cognitive impairment is commonly associated with the use of medication. This may cause temporary impairment of antegrade and retrograde memory, a transient global amnesia, fugue-like state or, much less commonly, a fixed and irreversible amnesia (Table 18.11).

Neuropsychiatric effects

The behavioural effects of medication may be difficult to assess and be non-specific. The development of listlessness, insomnia, drowsiness, restlessness, anxiety, euphoria or depression may be a manifestation of underlying disease or other metabolic or infective complications but a variety of medication does contribute; these include tricyclic antidepressants, amphetamines, phenothiazines, barbiturates, hypnotic, anticholinergics, antiepileptic medication and antihistamines. Similar features may be precipitated by acute withdrawal of medication. Affective disorders are less common but may be severe. A depressive reaction may occur during drug treatment. In the past, reserpine and methyldopa were recognized to cause depression. More commonly now depression occurs with other antihypertensive medication (clonidine, propranolol and calcium channel blocking drugs) but is also seen with corticosteroids, hypnotic agents, non-steroidal anti-inflammatory drugs, antituberculous medication, H2 antagonists, digoxin, baclofen, anabolic steroids, barbiturates and benzodiazepines.

Acute manic or hypomanic psychosis is unusual but may be associated with corticosteroids, thyroid replacement or, rarely, captopril, chloroquine and dopaminergic drugs.

Table 18.10 Drugs associated with encephalopathy.

Lithium	Diffuse disturbance of cerebral function associated with tremor, myoclonus, seizures, ataxia and confusion. Cerebellar dysfunction may persist
Psychotropic medication	Impairment of consciousness and memory with psychomotor activity is common, particularly with neuroleptics (e.g. haloperidol), tricyclic drugs, fluoxetine, venlafaxine
Anticholinergic medication	e.g. antiparkinsonian, antipsychotics, antihistamines, antiemetics, benzodiazepines
Drugs of abuse	e.g. cocaine, opiates
Histamine (H2) receptor antagonists	e.g. cimetidine
Non-steroidal anti-inflammatory drugs	
Opioid analgesics	Morphine and heroin
Others	Penicillins, cephalosporins, vigabatrin, valproic acid

Table 18.11 Drugs that may be associated with memory disturbance.

Chemotherapy
Anticholinergic medication
Antidepressants
Antiepileptic drugs
Analgesics drugs of abuse

Table 18.12 Drugs that may be associated with toxic leucoencephaolopathy.

Antineoplastic treatments	Cranial irradiation, methotrexate, cisplastin, cytarabine, levamisole, IL-2, interferon
Immunosuppressant	Tacrolimus, ciclosporin
Antimicrobial	Amphotericin B
Drugs of abuse	Toluene, ethanol, cocaine, amphetamine, ecstasy, heroin (iv, inhaled), psilocybin
Environmental toxins	Carbon monoxide, arsenic, carbon tetrachloride

Coma

This usually results from an inadvertent or deliberate overdose with hypnotic sedatives, antidepressants, analgesics or drug combinations. An overdose of insulin will also produce an acute hypoglycaemic coma and other drugs that may be implicated include phenothiazines, salicylates and valproic acid.

Sleep disorders

Sleep disorders resulting from medication may be manifest by excessive sleepiness, insomnia, sleep-related breathing disorders or parasomnias. Excessive drowsiness is associated with sedative, hypnotic or antidepressive medication and may also occur with antiepileptic drugs. Paradoxically, the same medication may also be associated with insomnia as may respiratory drugs including bronchodilators, cardiovascular drugs (antihypertensive medication, calcium channel blockers, beta-blockers and CNS stimulants). Vivid dreams and nightmares are often associated with drugs affecting noradrenaline, serotonin and dopamine neurotransmitters; these include the CNS stimulants, antipsychotic drugs and antiparkinsonian medication. Parasomnias may be related to the introduction of antipsychotic medication, sedative, hypnotics or antidepressants.

Toxic leucoencephalopthy

This is a disorder caused by a structural alteration of white matter caused by a variety of toxic insults usually related to therapeutic agents, illicit drug use and occupational exposure to toxins. The condition involves white matter tracts serving higher cerebral function and therefore presents with neurobehavioural disturbances including inattention, forgetfulness and changes in personality leading to somnolence, apathy, cognitive impairment and ultimately dementia, coma and death. MRI initially shows hyperintensity in the periventricular white matter but this progresses to a severe hyperintensity involving widespread white matter with necrotic areas. These changes are reflected in the pathology of patchy oedema within myelin which becomes widespread, leading to the destruction of oligodendrocytes, axonal loss and necrosis. The condition is associated with a variety of toxins listed in Table 18.12.

Cerebrovascular disease

Cerebrovascular disease may be associated with the use of drugs by a large number of potential mechanisms. There is a clear risk of haemorrhage as a complication of anticoagulant and thrombolytic therapies. Cerebral blood flow may be reduced particularly in elderly patients in the presence of cerebrovascular disease by any antihypertensive medication that reduces blood pressure below perfusion pressure. This may predispose to cerebral infarction in watershed territories. Cerebrovascular disease may be caused by direct neurotoxicity or indirect mechanisms such as involvement of other systems including cardiovascular, haematological, respiratory, renal, hepatic and metabolic or the presence of predisposing or coexisting general medical risk factors. A variety of medications may cause transiently elevated blood pressure including sildenafil, amphetamines, ephedrine, heroin and other drugs of abuse. Vasospasm may occur with sympathomimetics, triptans and cerebral vasculitis is particularly associated with amphetamines, ecstasy, penicillin, tacrolimus and occasionally allopurinol. There is a small increased risk of thrombo-embolism, ischaemic arterial or cerebral venous occlusion in women taking the oral contraceptive pill; chemotherapeutic agents including cisplatinum may also cause cerebral venous or arterial thrombosis or haemorrhage.

Impairment of taste and small

Disturbances of taste (dysgeusia) and smell (dysosmia) are extremely common manifestations of drug toxicity. They are particularly associated with antidiabetic therapy (oral hypoglycaemics), phosphodiesterase inhibitors, theophylline, caffeine, ethambutol, other antibiotics including penicillin, antirheumatic medication (gold, D-penicillamine), angiotensin converting enzyme inhibitors and many cytotoxic agents.

Drug-induced movement disorders

Several movement disorders are caused by commonly prescribed medication (Table 18.13). Acute dystonic and dyskinetic reactions often develop immediately following treatment and may be manifest as oromandibular dystonia, oculogyric crisis and opisthotonus. Dystonia may be more generalized with slow writhing movements of the limbs or prolonged contractions of the axial and limb musculature. The acute dystonias are usually self-limiting once the drug is discontinued. Akathisia is a state of motor restlessness characterized by an inability to keep the legs still and an urge to constantly move, pace or run. Akathisia usually remits within days or weeks following withdrawal

Table 18.13 Drug-induced movement disorders.

Acute dystonia	Neuroleptics (phenothiazines and butyrophenones) Tricyclic antidepressants Metoclopramide Antiepileptic drugs (phenytoin, carbamazepine) Others (propranolol, ondansitron and fluoxetine)
Akathisia	Phenothiazines, butyrophenones Benzodiazepines Antidepressants, SSRI (particularly fluoxetine)
Choreoathetosis	Antiepileptic medication Oral contraceptives Drugs of abuse e.g. crack cocaine Lithium
Parkinsonism	Dopamine receptor blocking drugs (e.g. phenothiazines and butyrophenones) SSRIs may induce or exacerbate parkinsonian syndromes
Tremor – essential and action	Sympathomimetics Tricyclic antidepressants, e.g. amitriptyline Other antidepressants Lithium Levodopa Caffeine, theophylline, aminophylline Hypoglycaemic drugs Antiepileptic drugs (valproate, phenytoin, carbamazepine, primidone) Sedatives, e.g. barbiturates, benzodiazepines
Tardive dyskinesia	Dopamine antagonists (especially antipsychotics) Metoclopramide Promethazine Prochlorperazine Antihistamines Tricyclic antidepressants Levodopa Monoamine oxidase inhibitors

of the neuroleptic drug but may occasionally persist or be permanent. Choreoathetosis is manifest as irregular multifocal non-stereotyped semi-purposeful jerky movements often associated with slower dystonic movements. Drug-induced tics are associated with amphetamine-like drugs, methylphenidate, haloperidol and other antipsychotic medication. Drug-induced parkinsonism is the most common form of iatrogenic movement disorder and may be extremely difficult to distinguish from idiopathic Parkinson's disease. The onset tends to be slow, with bradykinesis being the most prominent feature with variable rigidity, tremor and gait disturbance. The condition is usually reversible after drug withdrawal or dosage reduction over the course of several weeks but drugs may unmask latent idiopathic Parkinson's disease. A number of drugs may aggravate an essential or physiological tremor. Tardive dyskinesia usually develops after more than 12 months of continuous therapy but may evolve over a much shorter period, occasionally developing after cessation of therapy. It is characterized by orofaciobuccal dyskinesia with lip-smacking and pursing, jaw opening, closing and protrusion of the face with writhing movements of the tongue and facial grimacing. The movements tend to be stereotyped and may interfere with speech or swallowing. There may be associated choreoathetotic movements of the limbs and trunk with repetitive foot tapping. Tardive forms of tic, myoclonus and tremor are also described. A variety of dopamine receptor blocking drugs can cause tardive dyskinesiae; the newer atypical dopamine receptor blocking drugs, including clozapine, appear to carry less risk.

All the major classes of conventional neuroleptic drugs (phenothiazines, butyrophenones, thioxanthenes) and the atypical antipsychotic drugs including clozapine, olanzapine, quetiapine and risperidone have been described as causing extrapyramidal syndromes. All these side effects are idiosyncratic and patients vary greatly in their susceptibility and in the dose necessary to precipitate the side effects; patients with dementia with Lewy bodies are particularly susceptible.

Ototoxicity

Drug-induced damage to the cochlear and vestibular function is common. The former is manifest as tinnitus and hearing loss and the latter as vertigo, oscillopsia and imbalance. Both are characteristically associated with aminoglycoside antibiotics, gentamicin and streptomicin. Balance is usually preferentially affected. Loop diuretics, salicylates, antimalarials (quinine, chloroquine) and cytotoxic agents including cisplatin and vincristine may be associated with hearing loss (Chapter 14).

Cerebellar disorders

Cerebellar disorders are usually dose-related and reversible but may become fixed deficits after antiepileptic drugs, phenothiazides, lithium or ciclosporin.

Visual disorders

Drug-induced visual disorders may be brought about by a variety of different mechanisms and visual disorders.

- *Pupillary*: miosis is produced by parasympathetic drugs which include cholinergic agents (neostigmine, pyridostigmine) and opiates (morphine) but mydriasis, which may occur with anticholinergic agents (atropine, hyoscine), tricyclic antidepressants and phenothiazines (MAIOs, tricyclics), is a more serious drug effect because of the risk of precipitating closed angle glaucoma.
- *Distortion of the lens* may cause refractory changes because of fluid shifts with diuretics and antidiabetic therapy (insulin, oral hypoglycaemics) and corticosteroids.
- *Drug-induced retinopathy* may be caused by the development of pigmentary change (as occurs with chloroquine-like drugs and cardiac glycosides).
- *Macular oedema* (oral contraceptive) or visual field loss (e.g. ethambutol, indometacin, vigabatrin) may occur and optic neuropathy has been associated with some antibiotics (e.g. chloramphenicol, isoniazide, ethambutol, cytotoxic medication, opiates and non-steroidal anti-inflammatory drugs).
- *Nystagmus* is the most common drug-related eye movement disorder and is caused by antiepileptic drugs, tricyclic antidepressants, ototoxic medication, salicylates and MAOIs.

Autonomic effects

Disturbances of autonomic function are commonly caused by drug toxicity. Drug-induced syncope may occur as a consequence of vasovagal disturbances, postural hypotension or cardiac disease. Postural hypotension occurs with a variety of antihypertensive medication (particularly β-blockers, vasodilatators and diuretics), antidepressants and levodopa. In the elderly, syncope is particulary associated with fluoxetine, haloperidol and levodopa. Bladder disturbance occurs with anticholinergic medication (atropine, hyoscine), particularly with pre-existing prostatic outflow tract obstruction. Medication may cause sexual dysfunction at any level of function. Antihypertensive medication (β-blockers) is particularly associated with impotence or impairment of ejaculation, while antidepressant medication may affect libido or cause orgasmic dysfunction. Spinal toxicity may follow intrathecal injection of steroids, cytotoxic medication or contrast material leading to an infective or asceptic meningitis, adhesive arachnoiditis or direct toxic effects on the spinal cord or nerve roots. Epidural injection is not associated with these problems unless there is penetration of the dura.

Neuromuscular drug effects

There are many drugs that may cause non-specific fatigability but peripheral neuropathy is an extremely common manifestation of drug toxicity (Chapter 9).

Peripheral neuropathy

Most drug-related neuropathies are predominantly axonal (A) although demyelination (D) and conduction block may occur. Both motor and sensory patterns are seen. The major categories of drug-induced peripheral neuropathy are summarized in Table 18.14.

Table 18.14 Drugs causing peripheral neuropathy.

Antibiotics		**Neuropathy**
Metronidazole	A/D	Sensory
Nitrofurantoin	A	Sensorimotor or motor
Isoniazide	A	Sensorimotor or sensory
Ethambutol	A	Sensorimotor or motor
Dapsone	A	Motor
Antiviral nucleoside analogues	A	Sensory
Chemotherapeutic agents		
Cisplatin	A	Sensory
Vinca alkaloids	A	Sensorimotor ± autonomic
Cytarabin (high dose)	D	Sensory
Thalidomide	A	Sensory
Cardiovascular drugs		
Statins	A	Sensory > sensory motor
Amiodarone	A/D	Sensorimotor > motor
Enalapril	A	Sensorimotor > sensory
Hydralazine	A	Sensorimotor > sensory
Streptokinase	A	GBS-like syndrome
Antirheumatic drugs		
Gold	A/D	Motor > GBS-like
Chloroquine	D	Sensorimotor
Colchicine	A	Sensorimotor
Allopurinol	A/D	Sensorimotor
Others		
Tacrolimus	D	GBS-like
Ciclosporin	A	Sensory
Disulfiram	A	Sensorimotor
Lithium overdose	A	GBS-like
Phenytoin	A	Sensory and motor

A, axonal; D, demyelinating.

Table 18.15 Drugs that interfere with neuromuscular junction transmission.

Antibiotics	aminoglycosides, tetracycline, ciprofloxacin
Anti-arrhythmics	quinidine, procainamide
Antimalarials	chloroquine
Antirheumatics	pencillamine D
β-Blockers	propranolol, atenolol, metoprolol, sotalol
Antiepileptics	phenytoin
Neuroleptics	chlorpromazine, clozapine, flupenthixol, lithium, MAOIs
Muscle relaxants	

MAOIs, monoaminase oxidase inhibitors.

Drugs interfering with neuromuscular transmission

These may cause a myasthenic-like syndrome, uncover latent myasthenia or exacerbate the existing disease (Table 18.15). These are discussed in Chapter 9; only the most important drugs are listed in Table 18.15.

Muscle disease

A large variety of muscle diseases may be caused by drugs (Chapter 9).

Myalgia, stiffness and cramp

Many drugs cause myalgia, stiffness and cramp, often in association with a transiently elevated CK. Drug-induced myopathy may be associated with myotonia, pain or myokymia and may be focal or generalized. The most important drugs causing the different forms of myopathy are listed in Table 18.16.

Malignant hyperthermia

This condition occurs in susceptible individuals following anaesthesia using a halogenated inhaled anaesthetic (including halothane, enflurane and isoflurane) and/or a depolarizing muscle relaxant such as succinylcholine. The condition is characterized by the sudden onset of fever and rigidity associated with a high CK level with metabolic acidosis and myoglobinuria. Liability to malignant hyperthermia is transmitted in an autosomal dominant fashion and occurs in genetically predisposed individuals who have an intrinsic abnormality of the excitation–contraction coupling mechanism in skeletal muscle. This leads to an excessive release of Ca^{2+} from the sarcoplasmic reticulum resulting in myofibrillar contraction. The condition seems to be caused by a defect in the calcium release channel (RYR1) and the genetic basis is a mutation in the *RYR1* gene on chromosome 19q or in other calcium channel genes.

The onset of the condition is variable. In the most florid forms acidosis, rigidity and hyperpyrexia may develop within 30 minutes of anaesthesia but in some patients the onset is slower with the condition developing over several hours with only mild signs. The initial features are tachycardia, raised end tidal CO_2, metabolic acidosis and progressive muscular rigidity. The hyperthermia develops later but may be severe. In its most severe form the condition progresses to rhabdomyolysis and myoglobinuria, disseminated intravascular coagulation (DIC), cardiovascular collapse or hyperpyrexia leading to multi-system failure. There seems to be similar sensitivity to anaesthetic agents in patients with other neuromuscular diseases, in particular Duchenne muscular dystrophy, myotonia congenita, myotonic dystrophy, central core disease, congenital myopathy and osteogenesis imperfecta.

Vulnerability to this syndrome is suggested by a positive family history or previous difficulties during anaesthesia. It can be tested *in vitro* using biopsied muscle and observing a hypercontractile response to caffeine or halothane. Management involves the immediate discontinuation of the triggering anaesthesia and hyperventilation with 100% O_2 at high flow. Dantrolene is recommended as specific therapy in a dose of 2.5 mg/kg i.v. repeated as necessary. Supportive care of heart rate, temperature and oxygenation are essential. Core temperature can be reduced by ice lavage. Hyperkalaemia is managed by the use of bicarbonate, glucose, insulin and calcium but it is essential to be aware of rebound hypokalaemia which may precipitate further episodes. Myoglobinuria is treated with diuretics, fluid support and bicarbonate as necessary. With rapid and appropriate management the prognosis in an acute episode is good and the syndrome resolves rapidly. It is clearly essential to be aware of any susceptibility to this condition in planning anaesthesia. Complete recovery occurs in general but weakness may last for months after an acute episode.

Neuroleptic malignant syndrome

This is a serious and potentially fatal complication of treatment with antipsychotic agents. The condition is characterized by onset within 2 weeks of initiating or increasing neuroleptic therapy although, less commonly, it may develop after months or years of stable treatment. The signs evolve over up to 72 hours although the onset may be more acute and the condition usually resolves within 2 weeks. The onset is usually with progressive and severe pyrexia (>40°C in 40% of patients) although a more insidious onset with a modest pyrexia may occur. There is progressive encephalopathy and impairment of conscious state ranging from lethargy to delirium, confusion, agitation and coma. Severe 'lead pipe' rigidity with other extrapyramidal features including bradykinesis, rest tremor and dystonia develop. There is autonomic instability including tachycardia, tachypnoea, diaphoresis, labile blood pressure, skin pallor or flushing, sialorrhoea and urinary disturbance including incontinence. The condition is characterized by grossly elevated CK level and there is also usually a leucocytosis, metabolic acidosis and elevated CSF protein but muscle biopsy is non-specific.

The most common drugs causing this condition are haloperidol, fluphenazine and chlorpromazine but other phenathiazines, lithium, metoclopramide, tricyclic antidepressants or atypical antidepressants (clozapine, olanzapine) may also be responsible. Other risk factors seem to include the use of depot injections, high potency neuroleptics, rapid dose increase and the presence

Table 18.16 Drugs that cause muscle disease.

***Subacute necrotizing myopathy* – symmetrical proximal weakness with myalgia and elevated CK**
Amiodarone
Chloroquine
Lipid-lowering medication – simvastatin, pravastatin, atorvastatin
Colchicine
Corticosteroids
Zidovudine
Heroin
***Myositis* – inflammatory myopathy indistinguishable from polymyositis with elevated CK**
Chloroquine
Corticosteroids
D-penicillamine
Lipid-lowering drugs – simvastatin, pravastin
Others – phenyton, levodopa, cimetidine
***Myotonia* – drug either causing the myotonia or unmasking latent myotonic disorders**
Proprofol
Depolarizing muscle relaxants – suxamethonium
Diuretics – frusemide, acetazolomide
Vincristine
Lipid-lowering drugs – simvastatin, pravastatin
β-Blockers – propranolol, pindolol
***Focal fibrous myopathy following intramuscular drug injection* – caused by needle trauma and local effects of agent injected leading to severe muscle fibrosis and contractures**
Antibiotics
Chloroquine
Drug abuse
Myopathy caused by hypokalaemia
Diuretics
Purgative abuse
Licorice
Amphotericin B
***Mitochondrial myopathy* – characterized by myalgia, proximal weakness and elevated CK**
Zidovudine
***Rhabdomyolysis* – acute and severe necrotizing myopathy characterized by severe muscle pain, swelling and weakness leading to myoglobinuria and renal failure**
Anaesthetics
Lipid-lowering drugs – simvastatin, pravastatin
Diuretics
Barbiturates
Opiates – morphine, heroin
Alcohol
Other drugs of abuse – amphetamines, LSD

CK, creatine kinase; LSD, lysergic acid diethylamide.

of dehydration or agitation. There may also be a genetic predisposition to the condition. Despite treatment, neuroleptic malignant syndrome (NMS) may progress to the development of rhabdomyolysis leading to myoglobinuria and renal failure, coagulation defects from DIC, respiratory failure, shock, seizures and coma. In some series mortality has been up to 20%, with persisting neurological sequelae in 10% of survivors.

The management is both supportive and specific. The neuroleptic must be immediately discontinued and the core temperature normalized. There must be close attention to hydration, cardiac, respiratory and renal function with adequate anticoagulation. Specific management remains controversial. Dantrolene is a muscle relaxant that inhibits excitation contraction mechanisms and may influence central dopaminergic mechanisms in the active phase of NMS. It has been reported to be effective but there is a risk of hepatic toxicity. Bromocriptine is a dopamine agonist that works by acting centrally to counter the neuroleptic effects. It has been given in divided doses for up to 10 days after resolution of symptoms but its use is limited by side effects of nausea, hypertension and worsening mental state.

NMS probably results from a sudden decrease in central dopaminergic function resulting from profound dopamine receptor blockade at multiple sites including the corpus striatum and thermoregulatory and vasomotor centres in the hypothalamus. However, while the condition usually occurs with dopamine receptor blocking drugs it may also be seen with dopamine depleting drugs or even without exposure to neuroleptics.

Serotonin syndrome

Serotonin syndrome is a variable but potentially life-threatening drug reaction caused by excessive serotonin stimulation of the central and peripheral nervous systems. It results from therapeutic use, intentional self-poisoning or inadvertent interaction between drugs. Clinical manifestations are variable. There is a characteristic triad of mental state change, neuromuscular abnormalities and autonomic hyper-reactivity. The condition is probably more common than was previously thought particularly with increasing use of selective serotonin re-uptake inhibitors (SSRIs).

Presentation may be with mild tachycardia and minor autonomic features including shivering, diaphoresis and mydriasis. These may be considered to be simple drug reactions and the medication is often discontinued. However, in more severe forms the condition may progress to an intermittent tremor or myoclonus with hyper-reflexia. There may be severe hyperthermia, tachycardia and hypertension. Progressive encephalopathy with clouding of consciousness, confusion and hypomania may develop. Autonomic features that may evolve include mydriasis, hyperactive bowel sounds, diaphoresis and neurological involvement including the development of lead pipe rigidity, myoclonus, tremor, incoordination, clonus and hyper-reflexia. The condition usually develops within 24 hours of the initiation of causative medication but the onset may be within minutes or come on after several weeks at stable dosage.

Laboratory investigation may show metabolic acidosis, rhabdomyolysis, abnormalities of liver function and there may be features of DIC or renal failure but most cases are relatively minor and resolve over 12–24 hours. The condition occurs with monotherapy using SSRIs or when there is an interaction between two drugs from this class. These include SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) or other antidepressant drugs which inhibit the re-uptake of serotonin by other mechanisms including duloxetine, olanzapine, mirtazapine and venlafaxine. Serotonin syndrome may also be associated with other drugs that inhibit the re-uptake of serotonin and these are listed below. The condition has been reported to follow administration of a serotoninergic agent up to 5 weeks after discontinuation of fluoxetine.

Drugs that may cause serotonin syndrome either in isolation or when combined include:

- SSRIs;
- Atypical antidepressants;
- MAOIs – phenelzine and selegiline;
- Tricyclic antidepressants;
- Dopaminergic agents;
- Antiepileptic drugs – sodium valproate, carbamazepine;
- Lithium;
- Anaesthetics;
- Opiate analgesics – tramadol, meperidine, pentazocine;
- Risperidone;
- Over-the-counter cold remedies containing ephedrine and dextromethorphan;
- Antiemetics – ondansetron, metoclopramide;
- Antimigraine – sumatriptan and other triptans;
- Drugs of abuse – Ecstasy, opioids, LSD;
- Herbal products – St John's Wort;
- Withdrawal of medication.

The condition may be transient and not require treatment other than the discontinuation of the relevant medication. However, if the symptoms are severe, management is both supportive and specific. Following discontinuation of the serotoninergic medication it is necessary to control agitation, monitor the level of consciousness, respiratory and cardiac function and to control hyperthermia and autonomic instability. Sedation, neuromuscular paralysis and orotrachial intubation with ventilation may be necessary.

There remains controversy about specific treatment using 5-HT antagonists. A variety of treatments have been used but none is proven. The present recommendations are for the administration of cyproheptadine as it binds to 5-HT receptors. Chlorpromazine has also been used but there is no benefit from other 5-HT antagonists including lorazepam, methysergide and propranolol.

It is important to distinguish this condition from neuroleptic malignant syndrome, malignant hyperthermia, anticholinergic syndrome and the tyramine cheese reaction and this differential diagnosis is summarized in Table 18.17.

Table 18.17 Comparison of clinical features of serotonin syndrome, neuroleptic malignant syndrome (NMS), malignant hyperpyrexia, tyramine, anticholinergic syndrome.

		Serotonin syndrome	NMS	Malignant hyperpyrexia	Tyramine	Anticholinergic
Medication		Serotoninergic drugs	Dopamine agonists	Inhalation anaesthetic or succinylcholine	MAOI	Anticholinergic
Onset		<12 hours	1–3 days	30 m–24 hours	<12 hours	<12 hours
Vital signs	Temperature	++	+	++	+	+
	Blood pressure	+	+	+	++	±
	Pulse (tachycardia)	+	+	+	+	+
Systemic	Diaphoresis/skin	++	++	++	0	Dry
	Bowel sounds	Hyperactive	Normal	Normal/decreased	Normal	Absent
	Headache	+	0	0	+	++
	Flushing	+	+	+	+	++
Neurology	Mental state	++	++	+	+	++
	Mydriasis	+	0	0	0	++
	Rigidity	+	++	++	0	0
	Reflexes	++	+	0	0	Normal
	Myoclonus/tremor	++	+	0	0	0

MAOI, monoamine oxidase inhibitor.

Tyramine cheese reaction

The tyramine cheese reaction usually occurs in patients taking non-selective MAOIs. Ingestion of tyramine-containing substances (usually cheese or red wine) or sympathomimetic agents can lead to an acute hypertensive crisis, headache, nausea and vomiting culminating in hyperthermia and rarely DIC, renal failure and cardiopulmonary arrest. The condition is caused by excessive tyramine that has not been deaminated, leading to the release of catecholamines in nerve endings and the adrenal medulla. There may be progressive confusion and delirium which may evolve into coma. The patient appears flushed and may be pyrexial but there are no extrapyramidal features. Management is by withdrawal of the precipitating medication and supportive care.

Anticholinergic syndrome caused by medication toxicity

In this condition, mental state changes are common, usually beginning as a mild encephalopathy with disorientation but progression to profound clouding of consciousness and coma may occur. Anticholinergic features include mydriasis, dry oral mucosa and hot erythematous skin. In contrast to the serotonin syndrome there are reduced or absent bowel sounds and no extrapyramidal features. There is a tachycardia, increased respiratory rate and occasionally urinary retention. Management is with discontinuation of the causative drugs.

Other metabolic disorders

Porphyria

The porphyrias are a group of rare conditions mostly inherited in an autosomal dominant manner. They are caused by abnormal biosynthesis of haeme, which is a precursor of haemoglobin and cytochromes. The most commonly encountered disorder is caused by deficiency of the enzyme uroporphyrinogen synthetase leading to the overproduction and accumulation of the porphyrin precursors ALA (δ-aminolevulinic acid) and PBG (porphobilinogin) which are neurotoxic and lead to acute intermittent prophyria (AIP). Other forms of porphyria are caused by enzyme defects at other points in the synthetic pathway (Figure 18.8) leading to the accumulation of other porphyrin precursors.

AIP is characterized by recurrent attacks of acute abdominal pain and neuropsychiatric manifestations, generally from the teenage years onwards. There can be an acute or subacute, predominantly motor, polyneuropathy but no skin photosensitivity. AIP is characterized by symptom-free periods interrupted by acute neurovisceral attacks occurring with varying frequency. These episodes may be precipitated by a number of factors including drugs, calorie deficient diet, intercurrent infections, surgery or during the luteal phase of the menstrual cycle. Neurovisceral attacks are characterized by the acute onset of severe abdominal pain which is usually poorly localized and associated with nausea, vomiting, diarrhoea or constipation and features of an ileus. There is a secondary dysautonomia with hypertension, tachycardia, tremor, hyperhidrosis and urinary retention. Neuropsychiatric manifestations include anxiety, confusion, restlessness, agitation, insomnia and psychosis. There may be generalized seizures often in association with hyponatraemia. The polyneuropathy often follows neurovisceral attacks, but may occur independently, and is associated with back pain, prominent wasting and involvement of the proximal and cranial musculature. There may be occasional mild sensory features, but profound muscle weakness may progress to involve respiratory muscles, particularly the diaphragm. The diagnosis is established by finding elevated ALA and

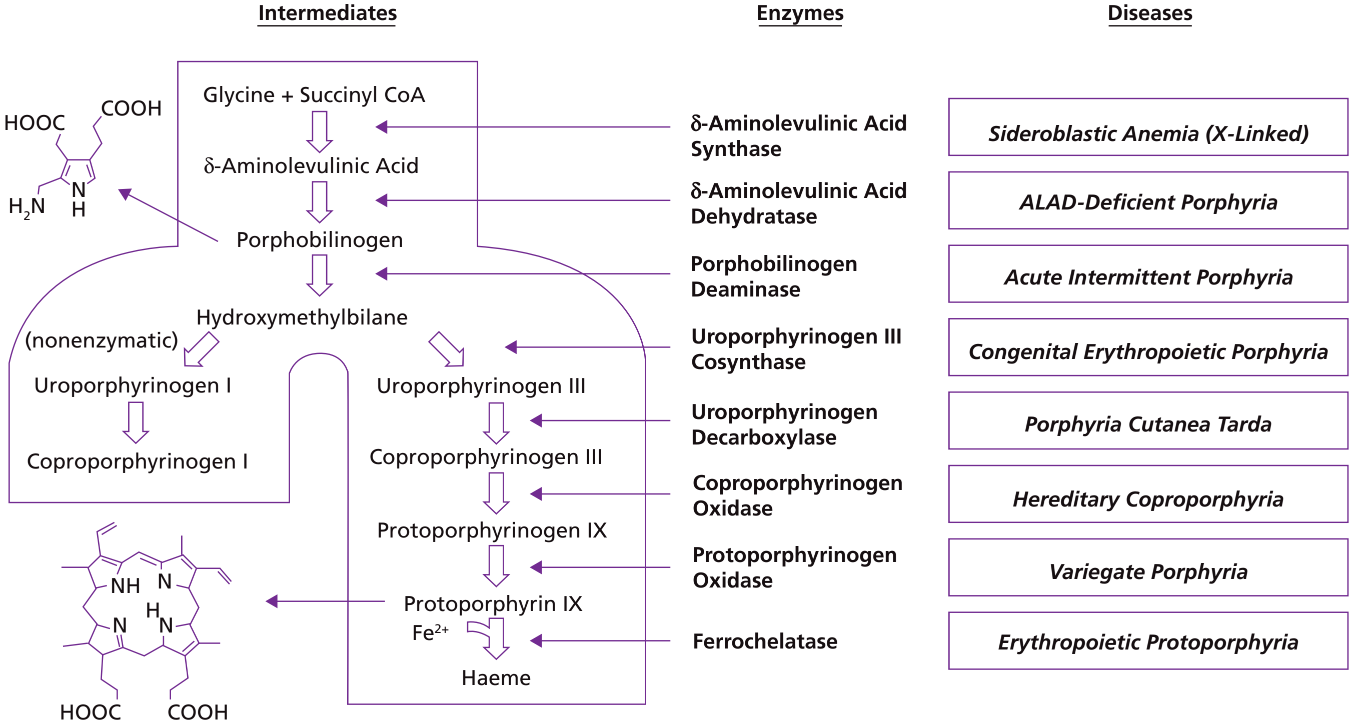

Intermediates
Enzymes
Diseases
HOOC
COOH
N
H
H_2N
Glycine + Succinyl CoA
δ-Aminolevulinic Acid
Porphobilinogen
Hydroxymethylbilane
(nonenzymatic)
Uroporphyrinogen I
Coproporphyrinogen I
Uroporphyrinogen III
Coproporphyrinogen III
Protoporphyrinogen IX
Protoporphyrin IX
Fe^{2+}
Haeme
NH
N
H
N
N
HOOC
COOH
δ-Aminolevulinic Acid Synthase
δ-Aminolevulinic Acid Dehydratase
Porphobilinogen Deaminase
Uroporphyrinogen III Cosynthase
Uroporphyrinogen Decarboxylase
Coproporphyrinogen Oxidase
Protoporphyrinogen Oxidase
Ferrochelatase
Sideroblastic Anemia (X-Linked)
ALAD-Deficient Porphyria
Acute Intermittent Porphyria
Congenital Erythropoietic Porphyria
Porphyria Cutanea Tarda
Hereditary Coproporphyria
Variegate Porphyria
Erythropoietic Protoporphyria

Figure 18.8 Metabolism of haeme showing enzyme deficiencies leading to specific porphyria syndromes.

porphobilinogin in the plasma and urine during an attack, although concentrations are not necessarily elevated between attacks. The greatest period of risk to patients is prior to the diagnosis being made when they and their physicians are unaware of the potential problems. Management is initially the prevention of attacks by avoiding precipitating factors. Treatment during an attack is both symptomatic and specific: symptomatic care involves the use of narcotic analgesics for abdominal pain; treatment of nausea, vomiting and agitation; correction of electrolyte disturbances; maintenance of high carbohydrate intake; and exclusion of underlying precipitating factors including infection. Specific treatment involves the use of intravenous haem arginate (Normosang) which acts by inhibiting ALA synthetase, the rate-limiting enzyme, allowing further metabolism along the pathway and leading to rapid resolution of symptoms and the abnormal excretion of metabolites. The most intriguing aspect of AIP is why relatively people with known mutations in the uroporphyrinogen synthetase become symptomatic.

Inborn errors of metabolism

This section deals with neurological disease seen in adult patients with inborn errors of metabolism. Whole textbooks have been written on the neurology of inherited metabolic diseases in children, but the combination of low incidence and high mortality rates means that the spectrum of disease seen in older patients is much more limited. The conditions described below do not make up a fully comprehensive list of all the inherited metabolic defects that can lead to neurological abnormalities in adults, but rather represent the conditions that are regularly encountered in a large adult metabolic clinic.

Lysosomal storage disorders (mucopolysaccharide and glycolipid disease)

Lysosomal storage disorders are caused by deficiencies of the cell's ability to degrade macromolecules (complex lipids, glycoproteins and mucopolysaccharides) within intracellular organelles (Table 18.18). Substances proximal to the metabolic block accumulate within the lysosomes and late endosomes and this storage leads to ultrastructural changes in the cell and pathological alterations to cell biology. The classic lysosomal storage disorders are caused by deficiencies in the activity of lysosomal hydrolases or their cofactors and are classified according to the type of storage material (e.g. sphingolipidoses, mucopolysaccharidoses, glycoproteinoses; Tables 18.18 and 18.19).

The lysosomal storage disorders are heterogeneous with the clinical phenotype depending on which tissues have the highest turnover of the storage material. Hence, in the mucopolysaccharidoses MPS I (Hurler's syndrome) and MPS II (Hunter's syndrome) there is storage of dermatan sulphate and severe skeletal involvement is prominent. However, in MPS III (Sanfilippo's syndrome), heparan sulphate is the glycosaminoglycan that is stored and the clinical features are predominantly of neurodegeneration.

Table 18.18 Lysosomal storage diseases.

Mucopolysaccharidosis
Type I (Hurler/Scheie)
Type II (Hunter)
Type III (Sanfilippo types A–D)
Type IV (Morquio)
Type VI (Maroteaux–Lamy)

Glycosphingolipidoses
GM1 gangliosidosis (juvenile and adult forms)
GM2 gangliosidosis (Sandhoff's disease)
GM3 gangliosidosis
Tay–Sachs disease
Gaucher's disease
Niemann–Pick's disease (A and B)
Niemann–Pick's disease (C and D)
Schindler's disease
Fabry's disease
Farber's disease
Krabbe's (globoid cell)
Metachromatic leucodystrophy

Oligosaccharidoses
Fucosidosis
Mannosidosis
Galactosialidosis

Mucolipidosis
Sialidosis
I-cell disease

Within each disease there is also marked variability of clinical phenotype. This is thought to relate in large part to the precise nature of the genetic mutation and the degree of residual activity of the affected enzyme. As a rule, the most severe mutations lead to early onset, rapidly progressive disease, while those with residual activity of even a few per cent may have a relatively attenuated, late onset presentation.

Many of the lysosomal storage disorders can lead to neurological involvement as summarized in Table 18.18. Some of the more common diseases are discussed in more detail below.

Glycosphingolipidoses

Glycosphingolipidoses (GSL) are derived from ceramide by sequential addition of sugar molecules. The GSL are a group of lysosomal storage disorders that result from an inability to degrade these complex lipids. As a group, they are the most common of the lysosomal storage disorders and all can involve the nervous system.

Gaucher's disease

Gaucher's disease, the most common of the GSL lysosomal storage disorders, is characterized by the accumulation of glucosylceramide within the lysosomes of cells. As with other lysosomal storage disorders, a broad spectrum of severity is seen in Gaucher's disease. Severe mutations that inactivate the glucocerebrosidase enzyme completely are not compatible with life and result in hydrops fetalis. Where there is minimal residual enzyme activity, glucosylceramide accumulates in a wide range of cell types, including neurones, and affected infants suffer a rapidly progressive neurological deterioration, so-called type 2 Gaucher's disease. In most patients, there is sufficient residual enzyme activity to fully degrade all glycosphingolipids in most cell types, including neurones. Significant storage is only observed in macrophages, which are exposed to a much greater load of GSL than other cells because of their role in phagocytosing other effete blood cells (most notably erythrocytes). These patients therefore have visceral disease resulting from infiltration of the liver, spleen and bone marrow with lipid-laden macrophages, but they do not have neurological involvement.

Between these two extremes are a group of patients with often severe visceral disease that is accompanied by more slowly progressive neuropathic disease, traditionally termed type 3 Gaucher's disease. These patients often present in childhood with a horizontal supranuclear gaze palsy. In more mildly affected patients this may be the only neurological manifestation, but a wide variety of other syndromes have been reported including myoclonic epilepsy, ataxia and dementia. More recently, an association has been described between type 1 Gaucher's disease and an early onset parkinsonian syndrome and it may be that neurological involvement in Gaucher's disease is more prevalent than has been previously appreciated.

Gaucher's disease was the first lysosomal storage disorder for which enzyme replacement therapy became available. Enzyme replacement therapy involves the intravenous infusion of recombinant glucocerebrosidase. This is efficiently taken up by Gaucher macrophages and is a highly effective treatment for non-neuropathic Gaucher's disease. However, because the recombinant molecule cannot cross the blood–brain barrier, enzyme replacement therapy has not been effective in treating neuropathic disease. Substrate reduction therapy (SRT) is an alternative approach that has been developed as a therapy for Gaucher's disease. SRT aims to reduce the rate of substrate synthesis to a level where the residual enzyme activity in a lysosomal storage disorder cell can clear storage and restore homeostasis. Miglustat, an imino sugar, is an inhibitor of the enzyme that catalyses the first step in glycolipid synthesis. Mice treated with miglustat exhibit up to 70% reduction in the glycolipid content of their tissues. In patients with type 1 Gaucher's disease, treatment with miglustat has been shown to reduce storage with significant reductions in organomegaly and markers of disease activity. Because miglustat is a small molecule that can penetrate the brain, it could potentially be used to treat neuropathic Gaucher's disease as well. Unfortunately, the limited results from trials available to date have been disappointing.

Fabry's disease (Anderson–Fabry disease)

This is an X-linked inborn error of metabolism caused by a deficiency of the lysosomal enzyme α-galactosidase, the gene for

Table 18.19 Neurological involvement in lysosomal storage diseases.

Disease	Mode of inheritance	Gene product	Storage material	Incidence	Clinical features	Treatment
MPS I	AR	α-L-iduronidase	Dermatan sulphate Heparan sulphate	1/75,000–85,000	Dysostosis multiplex resulting in compression neuropathies and myelopathy Corneal clouding Hepatosplenomegaly Cardiomyopathy Pneumonia Cognitive impairment	Bone marrow transplantation ERT for systemic features but does not affect CNS disease
MPS II	X-linked	Iduronate sulphatase	Dermatan sulphate Heparan sulphate	1/92,000–149,000 (males)	Dysostosis multiplex resulting in compression neuropathies and myelopathy Hepatosplenomegaly Valvular heart disease Obstructive sleep apnoea Cognitive impairment	ERT for systemic features but does not affect CNS disease
MPS III	AR	Heparan-*N*-sulphatase/ α-*N*-acetylglucosaminidase/acetyl-CoA: glucosamine-*N*-acetyltransferase/ *N*-acetylgllucosaminne-6-sulphatase	Heparan sulphate	1/86,000–114,000	Cognitive impairment Behaviour problems	Supportive treatment only
Gaucher's	AR	β-Glucocerebrosidase	Glucosyl ceramide	1/57,000–86,000	Hypersplenism Hepatomegaly Bone involvement Horizontal supranuclear gaze palsy Dementia Ataxia Spasticity Epilepsy Parkisonism	ERT for systemic features but does not affect CNS disease SRT could theoretically help neurological disease but clinical trials to date have been disappointing
Fabry's	X-linked	α-Galactosidase A	Ceramide trihexoside	1/117,000–833,000 but recent screening studies suggest incidence may be higher	Peripheral neuropathy Ischaemic stroke Dolichoectasia (elongation/fusiform dilatation of intracranial vessels)	ERT shown to reduce neuropathic pain. ERT has beneficial effects on cerebral perfusion; no effect on stroke incidence has been demonstrated.

Continued on p. 712

Table 18.19 *Continued*

Disease	Mode of inheritance	Gene product	Storage material	Incidence	Clinical features	Treatment
GM1-gangliosidosis	AR	β-Galactosidase	GM1	1/161,000–384,000	Dystonia Pyramidal signs Skeletal disease	Currently supportive Some early and encouraging reports of SRT with miglustat
GM2-gangliosidosis	AR	β-Hexosaminidase	GM2	1/32,000–384,000	Ataxia Dysarthria Spasticity Dementia	Currently supportive Some early and encouraging reports of SRT with miglustat
NP-C	AR	NP-C1/NP-C2	Cholesterol, GSLs	1/45,000–286,000	Ataxia Dystonia Dysarthria Dementia Psychiatric Vertical supranuclear ophthalmoplegia	Promising results from clinical trials of SRT with miglustat
MLD	AR	Arylsulphatase A	Sulfatide	1/54,000–92,000	Ataxia Spastic paraparesis Psychiatric Peripheral neuropathy Dementia	HSCT if performed early
GLD	AR	β-Galactocerebrosidase	Galactosylceramide Psychosine	1/74,000–201,000	Paraplegia or hemiplegia Ataxia Visual loss Peripheral neuropathy Dementia	HSCT if performed early

AR, autosomal recessive; ERT, enzyme replacement therapy; GLD, globoid cell leucodystrophy; GSL, glycosphingolipidosis; HSCT, haematopoeitic stem cell transplantation; MLD, metachromatic leucodystrophy; MPS, mucopolysaccharidosis; NP-C, Niemann–Pick's disease Type C; SRT, substrate reduction therapy.

Table 18.20 Clinical features of Fabry's disease.

Dermatology	Angiokeratoma corporis diffusum
	Individual ectatic blood vessels covered by a few layers of skin which may become hyperkeratotic. The lesions are usually flat or slightly raised and dark red to blue in colour. They are located in the groin, buttocks, upper legs and umbilical region. They become apparent in late childhood and increase in size and number over years
Cardiac	Affects myocardium, heart valves, conduction pathways and coronary vessels
	Hypertrophic obstructive cardiomyopathy
	Mitral valve insufficiency
	Endothelial storage in coronary vessels leading to myocardial ischaemia and infarction
Pulmonary	Dyspnoea, cough and wheeze
	Spontaneous pneumothorax, haemoptysis
Renal	Proteinuria with progression to chronic renal failure
Ophthalmology	Corneal opacities in the form of whorled streaks
	Lenticular opacities
	Retinal and conjunctival lesions manifest as tortuous and dilated vessels
	Inner ear damage
	Sensorineural hearing loss which may be sudden or gradual in onset causing vertigo and tinnitus
Peripheral nervous system	Acroparaesthesiae are characteristic burning or lancinating painful sensations occurring in the distal extremities usually developing in childhood
	Variable paraesthesiae and numbness in a 'glove and stocking' distribution
	Painful crises often triggered by exercise, fever, temperature change or stress lasting for several days, and associated with fever/elevated ESR
	Large fibre nerve conduction is usually normal but small fibre neuropathy may be present
	Autonomic neuropathy manifest as bowel disturbance (diarrhoea, constipation or nausea and hypohidrosis)

ESR, erythrocyte sedimentation rate.

which is localized at Xp22. This results in the accumulation of globotriaosylceramide (Gb3) in the vascular epithelium of many tissues including the kidney, heart, vascular endothelium, nervous system, eye and gastrointestinal tract. It is a multi-system disease which can manifest in the nervous system without systemic organ involvement and is an important cause of cerebral ischaemia in young people. Men are generally, but not always, more severely affected than women.

Clinical manifestations are summarized in Table 18.20. Clinical symptoms usually develop in early adolescence with the initial manifestations being the development of severe painful crises in the extremities, angiokeratoma, hypohidrosis, irritable bowel syndrome, and corneal and lenticular abnormalities. Progressive renal, cardiac and cerebral involvement then develops. Central nervous system involvement leads to an increased risk of ischaemic stroke with an earlier age of onset as a consequence of direct cardiac embolism or involvement of the cerebral vessels. There is a predeliction for the vertebro-basilar system where involvement is common over the age of 50 years. Posterior circulation stroke may be manifest as hemiparesis, vertigo, diplopia, nystagmus, dysarthria or ataxia. The diagnosis depends on the measurement of reduced α-galactosidase A enzyme activity measured in plasma leucocytes, cultured fibroblasts or transformed lymphoblasts. Skin biopsy may show intralysosomal lipid deposition in clinically normal areas of skin. Nerve conduction study is usually normal but may show evidence of a small fibre neuropathy and CSF may show high levels of glycolipids. If there are diagnostic difficulties DNA analysis may be necessary. Fabry's disease has a poor prognosis with most untreated males dying by the age of 40 years, generally from renal failure although myocardial infarction and cerebrovascular disease can also cause fatal complications. The life expectancy is reduced slightly in heterozygos female carriers.

Management

Symptomatic treatment of the painful acroparaesthesiae requires carbamazepine, gabapentin, pregabalin or even low doses of opiates. Progressive renal failure may require transplantation and skin lesions are treated by laser coagulation of small and medium sized vessels. Conventional stroke protection with antiplatelet drugs or anticoagulation may be effective. Enzyme replacement has been developed to treat the condition. It appears to be well tolerated and is effective in improving neuropathic pain and stabilizing renal function. Two enzyme preparations are now available: agalsidase α and β. These are safe and well tolerated but are expensive; they seem to be effective in slowing the progression of renal disease but have less benefit on the small fibre polyneuropathy. Both are given as intravenous infusions once a fortnight. The possibility of gene transfer is being actively pursued.

GM2 gangliosidosis

GM2 gangliosidosis is caused by mutations in the genes encoding the subunits of β-hexosaminidase. Mutation of the *HEXA* gene leads to Tay–Sachs disease and of the *HEXB* gene to Sandhoff's disease. β-hexosaminidase cleaves the terminal galactose residue from GM2 ganglioside. As GM2 ganglioside is predominantly expressed in neurones, the GM2 gangliosidoses are predominantly neurodegenerative disorders.

As with the other lysosomal storage disorders, there is a spectrum of disease severity. The classic infant forms present within the first 6 months of life with seizures, blindness and developmental delay and are rapidly fatal. Although rare in the general population, certain ethnic groups have much higher incidences. In Ashkenazi Jewish populations, where the carrier frequency for Tay–Sachs disease is 1/30 (compared to 1/300 for the general population), carrier screening programmes have dramatically reduced the numbers of babies affected.

The late onset forms of GM2 gangliosidosis can present in childhood or adulthood with gait problems, dystonia and bulbospinal neuropathy mimicking motor neurone disease. The disease is slowly progressive with dysarthria and gradual cognitive decline until patients eventually succumb to respiratory infections secondary to dysphagia. The diagnosis is made by assaying the activity of β-hexosaminidase in peripheral blood leucocytes.

Brain imaging shows striking cerebellar degeneration which is secondary to loss of Purkinje cells. Histologically there is neuraxonal dystrophy, characterized by the formation of axonal spheroids and meganeurites with ectopic dendritogenesis, which is also seen in other lysosomal storage disorders in which there is ganglioside storage within neurones.

Currently, therapy is supportive. SRT with miglustat has been shown to prolong life in a knockout mouse model of Sandhoff's disease and there are case reports of its use in patients with GM2 gangliosidosis, although no formal clinical trials have been conducted.

Metachromatic leucodystrophy and globoid cell leucodystrophy (Krabbe's disease)

These are GSL storage diseases that primarily cause white matter disease. Metachromatic leucodystrophy (MLD) is caused by deficiency of arylsulfatase A, a lysosomal hydrolase, which leads to the accumulation of sulfatide. Deficiency of the next enzyme in the degradative pathway, β-galactocerebrosidase, which converts galactosylceramide to ceramide, is the cause of globoid cell leucodystrophy (GLD). In MLD, storage of sulfatide, a component of myelin, in oligodendrocytes and Schwann cells leads to progressive central and peripheral nervous system demyelination. Although there is storage in other tissues (kidney, gallbladder, liver), the clinical features relate to nervous system involvement. As with other lysosomal storage disorders, there is a spectrum of disease ranging between severe infantile onset and more attenuated adult onset forms. Late onset forms of MLD can have either a neurological presentation, often with gait problems resulting from cerebellar involvement and a progressive spastic paraparesis, or a psychiatric presentation which often results in misdiagnosis as schizophrenia or an affective disorder. Recent studies have shown that these two presentations may be associated with different genotypes. In both types, MRI shows diffuse areas of demyelination in the subcortical and periventricular white matter. The diagnosis is confirmed by measuring arylsulfatase A activity in peripheral blood leucocytes.

GLD also affects myelin. In the most severe infantile onset cases there is an almost complete loss of myelin and oligodendrocytes throughout the brain which is accompanied by infiltration by the pathognomic globoid cells, which are galactosylceramide-laden macrophages. However, accumulation of galactosylceramide is not cytotoxic and cannot account for the loss of myelinating cells. Instead, it is thought that the oligodendrocytes are exquisitely sensitive to psychosine, a related compound which is also a substrate for β-galactocerebrosidase. Psychosine is barely detectable in normal brain, but accumulates in the brains of GLD patients. Late onset GLD can be variable in presentation, especially in adult patients, but the most common features are paraplegia or hemiplegia, cerebellar ataxia, visual loss, peripheral neuropathy and dementia. Although there may be an initial rapid deterioration, the disease is generally very slowly progressive in adult patients. MRI shows evidence of demyelination, commonly involving the pyramidal tract, corpus callosum and parieto-occipital white matter. In advanced disease there is diffuse symmetrical cortical atrophy. Diagnosis is confirmed by enzyme assay in leucocytes.

Allogeneic haematopoeitic stem cell transplantation (HSCT) has been used to treat both MLD and GLD. The rationale behind this approach is that microglia derived from donor stem cells can repopulate the CNS where they can act as an enzyme factory, secreting active enzyme which is then taken up by surrounding host cells where it can degrade substrate and reverse storage. As it takes considerable time for the brain to be repopulated in this way, HSCT is of limited use in the early onset, rapidly progressive forms of disease, although recent studies have suggested that when infants affected by GLD are identified by screening and transplanted within the first week of life, outcomes can be very good. Disease stabilization does seem to be possible in late onset patients, provided that they are transplanted early enough. However, results are not always good, particularly in MLD where peripheral nerve involvement continues to progress, and the procedure itself is associated with significant morbidity and mortality.

Niemann-Pick's disease Type C

Niemann–Pick's disease Type C (NP-C) is a neurovisceral lysosomal lipid storage disorder which has marked similarities to the glycosphingolipidoses. NP-C is a disorder of lipid trafficking in which cholesterol, glycolipids and other molecules are unable to exit the late endosomal/lysosomal compartment of the cell. In 95% of cases, the disease is caused by mutations in *NPC1*, which encodes an integral membrane protein localized to the late endosomal/lysosomal compartment. The remaining 5% of patients have a deficiency of NP-C2, a soluble lysosomal glycoprotein whose precise function is not currently known. Clinically significant disease is confined to the liver, spleen, lungs and brain. NP-C can present with cholestatic jaundice and hepatosplenomegaly in the neonatal period. In the most severe form, there is early death from liver or respiratory failure, but in most cases the liver disease resolves and neurological involvement becomes the predominant feature. Classically, children present in their early school years with learning difficulties and cerebellar ataxia. Vertical supranuclear ophthalmoplegia is commonly present at an early stage. The course of the disease is progressive with the development of spasticity, dysarthria and dysphagia, dystonia and dementia. Cataplexy and gelastic seizures are typical. Patients usually die in their teens or early twenties.

Although the clinical features are similar to those seen in childhood disease, patients presenting with the adult form of the condition have a more insidious onset and gradual progression. In one large series of patients presenting at the age 15 or older, in 38% of cases the first symptoms were psychiatric (psychosis, affective disorders, obsessive-compulsive disorders); 23% presented with cognitive dysfunction, 20% with cerebellar ataxia and 11% with a movement disorder. Vertical supranuclear ophthalmoplegia was only present in 8% of patients at presentation. For this cohort, it took on average 6 years for the diagnosis of NP-C to be made and the patients survived for a mean of 13 years after first presentation. Diagnosis of NP-C relies on the demonstration of cholesterol storage and abnormal cholesterol esterification in cultured skin fibroblasts. Where there is splenomegaly, a full blood count may show evidence of hypersplenism. Even when the liver is enlarged, liver enzymes are rarely elevated. The plasma chitotriosidase can be elevated up to twofold above the normal range. Neuroimaging shows atrophy which becomes more pronounced as the disease progresses, but there are no specific radiological findings.

Treatment is symptomatic and palliative. Where seizures occur, they can be difficult to control. As the disease progresses, patients can develop severe sleep disturbance; this can respond to melatonin. Progressive dysphagia often necessitates the insertion of a gastrostomy tube for feeding. It has been shown that treatment with miglustat can reverse lysosomal storage in peripheral blood lymphocytes; further clinical trials are currently underway.

Disorders of carbohydrate metabolism

Glycogen storage diseases

Glycogen storage disorders (Table 18.21) can be divided into those that predominantly affect the liver (types I, III, VI and IX) and those mainly affecting muscle (types II, IV, V and VII). The hepatic forms do not generally have neurological manifestations apart from the consequences of severe prolonged hypoglycaemia which can cause encephalopathy, seizures and even death.

Management involves maintaining glucose homostasis by providing exogenous glucose in the form of uncooked cornstarch and/or continuous ovenight glucose pump feeds. The majority of patients with GSD type III, caused by glycogen debrancher deficiency, develop a mild distal skeletal myopathy in later life which rarely causes significant clinical problems. Rare patients with this disorder can develop a peripheral neuropathy.

GSD type II is caused by lysosomal acid maltase deficiency and can either cause infantile Pompe's disease with a significant cardiomyopathy and generalized myopathy, or late onset disease with a limb girdle dystrophy presenting in later childhood or adulthood. Without specific therapy, Pompe's disease is invariably fatal. Late onset acid maltase deficiency causes progressive weakness with diaphragmatic involvement and leads to death following respiratory failure. Since 2006, enzyme therapy for this condition has become available which is changing the natural history of the disorder. GSD type IV, caused by glycogen branching enzyme deficiency, is a very rare disorder that can present in various forms including cirrhosis and liver failure, or a generalized myopathy associated with polyglucosan bodies. Diagnosis is made on histopathological findings on muscle biopsy and appropriate enzymatic studies. Apart from liver transplantation, no specific therapy is available.

Table 18.21 Defects in carbohydrate metabolism.

Glycogen storage disease
Type I (von Gierke's disease)
Type II (Pompe's disease)
Type III (Cori's disease)
Type IV (Andersen's disease)
Type V (McArdle's disease)
Type VI (Hers's disease)
Type VII (Tarui's disease)
Type IX (phosphorylase b kinase deficiency)
Fructose, galactose and glycerol disorders
Hereditary fructose intolerance
Fructosuria
Galactosaemia
Hyperglycerolaemia (glycerol kinase deficiency)

GSD types V and VII both present with myalgia in later life, the later can also be associated with rhabdomyolysis. Patients with GSD type V often display a 'second wind' phenomenon whereby they can continue to exercise through pain into a painless phase. Rare patients can develop a slowly progressive limb girdle dystrophic picture. The disorders can be distinguished by enzymatic studies on muscle biopsy material. Apart from providing exogenous glucose or sucrose during intercurrent illnesses and careful exercise programmes, there is no specific therapy known to be effective.

Galactosaemia

In healthy individuals, galactose is metabolized to UDP-glucose (the Leloir pathway). Classic galactosaemia is caused by deficiency of galactose-1-phosphate uridyltransferase (GALT), which converts galactose-1-phosphate to UDP-galactose, which is subsequently epimerized to UDP-glucose. Galactosaemia has autosomal recessive inheritance and occurs with an incidence of about 1/40,000 in Europe. The diagnosis is made by measuring red blood cell GALT activity. It presents with acute liver damage within a few days of the first milk feed. Babies may then go on to develop sepsis and encephalopathy and the condition is fatal if galactose is not withdrawn from the diet. Once on a milk-free diet the acute metabolic abnormalities rapidly resolve, but patients may experience a number of complications in the medium to long term.

The majority of female patients develop hypogonadotrophic hypogonadism, which can be primary or secondary. Progress through puberty needs to be carefully monitored. Oestrogen deficiency contributes to the high incidence of osteoporosis that occurs in this population, but male patients with galactosaemia are also prone to low bone mineral density and dietary calcium deficiency is also important. Galactosaemia also has effects on the brain. Many studies have shown that IQ scores are below normal in children and adults with galactosaemia. Some cross-sectional and longitudinal studies have suggested that IQ may fall over time. Verbal dyspraxia has been reported in up to 62% of patients. Ten to 20% of patients have tremor and ataxia, and this can be progressive.

All of these complications are seen in patients who are taking a galactose-free diet and do not seem to correlate with how early the diagnosis was made, when treatment was initiated or with dietary compliance. Indeed, it is not uncommon for second-born children to have a worse outcome than their older siblings even if they have never ingested galactose, suggesting the possibility of antenatal damage. It has also been suggested that endogenous production of galactose may result in a low level accumulation of potentially toxic metabolites which result in ongoing damage to the brain. However, a patient has been reported who was on an unrestricted diet from the age of 3 who had a neurological outcome that was no worse than the majority of treated patients, and who did not develop osteoporosis. This would suggest that, after infancy, dietary restriction may not be important, either because, as they develop, the organs can better tolerate the accumulation of potentially toxic metabolites of galactose, or because alternative pathways of galactose metabolism are up-regulated.

Disorders of amino acid catabolism

There are many disorders of amino acid catabolism, both of enzymatic deficiencies within the degradative pathways of specific amino acids such as phenylketonuria or within pathways using common products of catabolism, such as the urea cycle disorders (Table 18.22). Bioactive amines such as tryptophan, glycine and glutamine have a fundamental role in neurotransmission and disorders involving such metabolites not surprisingly result in devastating disease. Systemic inborn errors of amino acid catabolism can produce neurotoxic metabolites such as ammonia also leading to fatal cerebral oedema.

Phenylketonuria

Phenylketonuria (PKU) is one of the most common inherited metabolic disorders, with an incidence of about 1/10,000 live births. The majority of cases result from deficiency of phenylalanine hydroxylase (PAH) which converts phenylalanine into tyrosine. More rarely, deficiency of tetrahydrobiopterin (a cofactor of PAH) is responsible.

Table 18.22 Disorders of amino acid and organic acid metabolism.

Specific amino acids
Phenylketonuria
Tyrosinaemia (Types I–III)
Alcaptonuria
Homocystinuria
Maple syrup urine disease
Urea cycle defects
Hyperammonaemias
Carbamoyl phosphate synthetase (CPS-I) deficiency
Ornithine transcarbamylase deficiency
N-acetylglutamate synthetase deficiency
Argininosuccinic aciduria
Hyperargininaemia
Citrullinaemia
Ornithine aminotransferase deficiency
Defects in amino acid transport
Cystinuria (Types I & III)
Hartnup's disease
Defects in organic acid metabolism
Fatty acid oxidation defects
Glutaric aciduria type I
Methylmalonic acidaemia
Proprionic acidaemia
Isovaleric acidaemia

The infant brain is sensitive to high phenylalanine levels and, if left untreated, PKU gives rise to severe mental retardation. Microcephaly is common and about 25% of patients have epilepsy. In older patients, behavioural problems are common and some have psychotic illnesses. A few patients develop movement disorders with pyramidal and extrapyramidal signs. Although most of the pathology is related to brain damage, eczema is also common. Because of a deficiency in melanin formation (because of tyrosine deficiency), patients tend to be fair skinned with blond hair and blue eyes.

The evidence suggests that phenylalanine itself is toxic to the developing brain. In rare patients who have normal IQ despite very high plasma phenylalanine concentrations, magnetic resonance spectroscopy (MRS) has shown that phenylalanine concentrations in the brain are normal. Like other large neutral amino acids, phenylalanine is actively transported into the brain by the L-type amino acid carrier. It has been suggested that genetic variance in this transport system might account for the phenotypic variability seen between PKU patients with similar plasma concentrations of phenylalanine but, to date, no evidence for this has been found.

The mechanism by which phenylalanine causes damage to the developing brain has not been elucidated. It has been suggested that abnormalities in neurotransmitters, particularly dopamine, which is derived from tyrosine, the levels of which can be low in PKU, might be involved. Imaging studies have shown high signal in the periventricular white matter, but this observation seems to relate directly to the brain concentration of phenylalanine and does not appear to have any functional consequences.

Provided the diagnosis is made soon after birth as part of a neonatal screening programme, PKU can be effectively treated by strict limitation of phenylalanine in the diet. This is achieved by restricting dietary protein intake and providing phenylalanine-free amino acid supplements. It is also necessary to supplement the vitamins, minerals and other micronutrients that are usually obtained from meat and dairy products (e.g. vitamin B_{12}, calcium and iron). The amount of dietary protein allowed is titrated against blood phenylalanine concentrations which vary according to residual PAH enzyme activity which in turn is a function of the genotype. In infancy and early childhood, metabolic control needs to be strict in order to protect the developing brain and, in the UK, practice is to keep the phenylalanine level <360–480 μmol/L (normal range 33–81 μmol/L).

There is evidence that children who are taken off a protein-restricted diet after 10 years of age will have IQ in the normal range when tested later in life, implying that the brain becomes resistant to the toxic effects of phenylalanine as it matures. However, other studies have shown more subtle cognitive deficits in adult patients not on a protein-restricted diet when compared with those who have followed a diet throughout life. Current practice in the UK is to encourage patients to follow a protein-restricted diet throughout childhood. Once they reach adulthood, however, and often before, many patients choose to resume a normal diet, and their phenylalanine concentrations rise accordingly. There is currently no evidence that this poses any risk of irreversible neurological damage. There have been some reports of spastic paraparesis developing in untreated patients, but these seem to have been secondary to vitamin B_{12} deficiency. Some patients are particularly susceptible to nutritional deficiencies as, even when dietary restrictions have been lifted, they still avoid high protein foods and follow a diet of poor nutritional quality. In these cases, it is important to monitor nutritional status carefully and continue with appropriate vitamin supplementation.

Some neuropsychological studies have described problems with executive functioning and speed of processing in children and adolescents both on and off a protein restricted diet. These observations have led to a recommendation of 'diet for life'. However, there is no consensus on what phenylalanine concentration should be achieved in an adult patient following a protein restricted diet with targets ranging from <600 μmol/L in the USA to 1300 μmol/L in France. In our clinic we aim to keep phenylalanine <700 μmol/L but, in reality, only a minority of patients are able to achieve this.

Maple syrup urine disease

Maple syrup urine disease (MSUD) is a defect of catabolism of the branched-chain amino acids valine, leucine and isoleucine, caused by deficiency of branched-chain α-ketoacid dehydrogenase (BCKD). MSUD derives its name from the aroma of the accumulated ketoacids excreted in urine. Classic untreated MSUD, with complete deficiency of BCKD, usually presents in the first week of life with non-specific symptoms which rapidly progress to encephalopathy and death. Partial enzyme activity can result in an intermediate phenotype resulting in either or both developmental delay and intermittent acute encephalopathic episodes.

Neurotoxicity is directly related to the degree and duration of elevation of the plasma leucine, while elevations in isoleucine and valine appear to have no significant impact. Acute leucine intoxication is characterized by decreased cognitive ability, hyperactivity, hallucinations, dystonia, ataxia and stupor. There is some evidence to suggest that leucine competitively inhibits other large neutral amino acids (LNAA) transport across the blood–brain barrier. The elevated plasma concentrations of leucine caused by MSUD, and low concentrations of most other amino acids because of protein restriction, perpetuate decreased concentrations of CSF LNAA such as tyrosine. Low cerebral tyrosine is implicated in acute symptoms such as choreoathetosis, dystonia and phenothiazine sensitivity. Chronic cerebral protein deficiency has resulted in paucity of dendritic branching and suboptimal myelination in patients with protein malnutrition and poorly treated MSUD and PKU.

With timely treatment, death and neuro-disability can be avoided even in the severe classic forms of MSUD. In keeping with many inborn errors of metabolism, the principles of treatment are:

- Restrict dietary protein sufficient only for basal requirements (and growth in childhood);
- Prevent protein catabolism at times of fasting or physiological stress using a high carbohydrate emergency regimen; and
- Supplement diet with trace elements and amino acids not affected by the disorder.

In practice, patients require active dietary management, titrating protein intake with blood BCAA concentrations, particularly in childhood. Quite apart from surplus protein resulting in elevation of leucine, insufficient energy for the body's requirements leads to catabolism and elevations of BCAA. Because of the dietary protein restriction, additional energy sources from carbohydrates or fat may be required to meet these requirements. Encephalopathic patients with gross elevations of plasma leucine >1500 μmol/L (normally 70–200 μmol/L) can respond well to haemodialysis.

Several countries worldwide now screen for MSUD as part of their newborn screening programmes when blood spots are collected on day 1 or 2 of life. Provided that intervention in the newborn period is intensively managed, with haemodialysis if necessary, the prognosis is good. Normal intellectual ability is possible, but this outcome is dependent on meticulous long-term dietary treatment with expectant management of intercurrent illnesses.

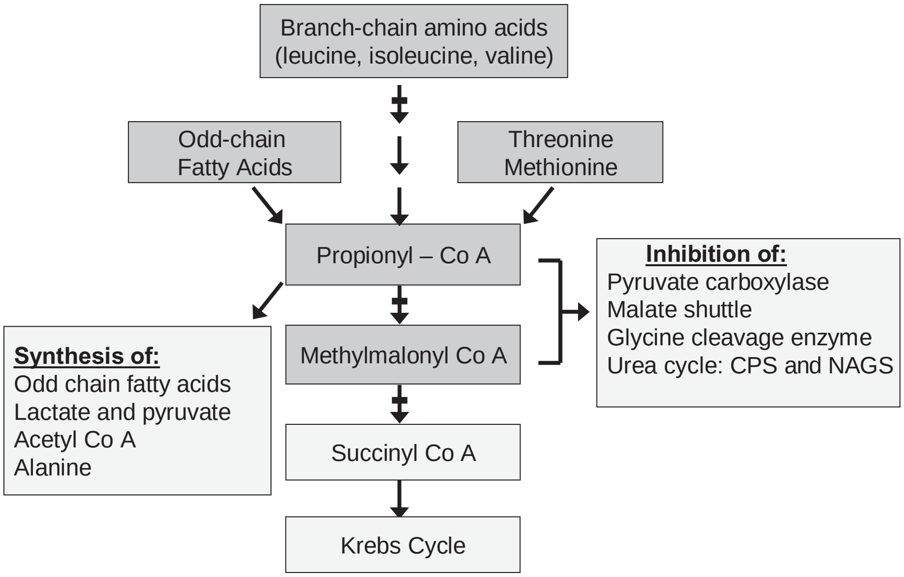


Figure 18.9 Organic acidaemias and their metabolic consequences.

Methylmalonic acidaemia and propionic acidaemia

Propionic and methylmalonic acid are biochemical intermediaries of BCAA degradation, and both have fundamental roles in energy production. These organic acids also have roles in the degradation of other amino acids, fatty acid metabolism, the Krebs cycle, gluconeogenesis and the detoxification of ammonia (Figure 18.9). Complete deficiency of either propionyl CoA carboxylase or methylmalonyl CoA mutase (mut 0) results in severe neonatal encephalopathy, often fatal. Partial deficiency or defects in the synthesis of the respective cofactors biotin or adenosylcobalamin may present either in a similar manner or subacutely, but are more amenable to treatment.

Classic methylmalonic acidaemia (MMA) and proprionic aciaemia (PA) present in the neonatal period with non-specific signs that rapidly progress to lethargy, seizures and coma in the first week of life. Patients typically demonstrate a severe metabolic acidosis with increased anion gap, ketonuria as well as a variable pancytopenia and hyperammonaemia. The blood glucose is sometimes decreased or occasionally increased. Intermediate phenotypes including cofactor defects may present later in life with acute encephalopathy, developmental delay, movement disorder or behavioural disturbance. Quite apart from the severe neurological insult in some patients with these diseases, others have specific insults to the basal ganglia resulting in choreoathetosis with compatible radiological findings.

Urine organic acids measured by gas chromatography mass spectrometry demonstrate elevations of propionate and methylcitrate in both disorders, but methylmalonate is not found in PA. However, methylmalonate may also be seen in the urine of patients with vitamin B_{12} deficiency. The clinical context and supporting biochemistry need to be considered together before definitive enzyme assays from cultured skin fibroblasts are performed.

These organic acidaemias need to be considered in all neonates who present with progressive encephalopathy in the first 2 weeks of life, particularly if acidosis, ketonuria and hyperammonaemia are associated with these findings. Some patients respond to administration of intravenous biotin (PA) or intramuscular vitamin B_{12} (MMA) and these should be administered urgently after diagnostic urine and plasma samples are taken, and continued if the patient remains symptomatic. Subsequent treatment follows the same general principles of amino acidopathies: protein restriction, prevention of catabolism and supplementation of trace elements.

Both diseases require surveillance for long-term problems. Acute pancreatitis, cardiomyopathy and osteopenia occur in both conditions. Progressive renal glomerular and tubular disease are specific features of MMA and in some cases can be very aggressive in childhood. Renal failure is a common occurrence in patients with MMA. Despite optimal management, some patients with either PA or MMA can still decompensate and become encephalopathic for reasons that are not clear. Others can present with catastrophic metablic stroke. Therefore the overall prognosis remains guarded, but some patients with cofactor responsive disease in particular fare much better.

Fatty acid oxidation defects

Mitochondrial oxidation of fat is an important energy source for many tissues, especially during fasting or sustained aerobic exercise. At these times, long-chain fatty acids are released from triglyceride stores in adipose tissue and transported to other tissues in the blood. Short- and medium-chain fatty acids can diffuse across the mitochondrial membrane, but long-chain fatty acids require a specific transport mechanism. Long-chain acyl-CoA compounds are conjugated with carnitine to form acylcarnitines, which are then transported into the mitochondrial matrix

Table 18.23 Fatty acid oxidation defects.

Errors in mitochondrial fatty acid oxidation
Disorders of β-oxidation
Very long-chain acyl-CoA dehydrogenase deficiency
Short, medium and long-chain acyl-CoA dehydrogenase deficiency
Carnitine translocase deficiency
Carnitine palmitoyltransferase I (CPT I) deficiency
Carnitine palmitoyltransferase II (CPT II) deficiency
Disorders of carnitine-mediated transport and carnitine uptake

by carnitine palmitoyltransferases (CPTs). Once inside the mitochondria, the carnitine is recycled to the cytoplasm and the acyl-CoA esters enter the β-oxidation pathway. Each β-oxidation cycle shortens the acyl chain by two carbon atoms and results in the production of one molecule of acetyl-CoA which can then enter the tricarboxylic acid (TCA) cycle or, in the liver, be used to generate ketone bodies.

About 15 inherited fatty acid oxidation (FAO) disorders have been described (Table 18.23). Many of these are life-threatening diseases of childhood and present with hypoketotic hypoglycaemia, encephalopathy and hepatic dysfunction. Only the milder defects affect adult patients, causing exercise intolerance, episodic rhabdomyolysis and neuropathy.

Although resting skeletal muscle relies on low level FAO for energy, during exercise there is a switch to utilizing muscle stores of glycogen. Once these have been depleted (after about 5–10 minutes), the main fuels become the muscles' stores of triglycerides and glucose from the circulation. As exercise continues, the supply of free fatty acids becomes more important and, after about an hour, mitochondrial FAO is once again the major source of energy for muscle. In the milder FAO defects, residual FAO is adequate to supply the resting energy requirements of muscle, but is insufficient during extended exercise, resulting in muscle cell death and rhabdomyolysis.

Carnitine palmitoyltransferase Type II deficiency

Carnitine palmitoyltransferase Type II deficiency (CPTII) is responsible for the transfer of acylcarnitines across the inner mitochondrial membrane. Although the more severe forms of CPTII deficiency present with severe liver disease in infancy, there is also a late onset muscular form. This is characterized by myalgia and rhabdomyolysis which can be triggered by exercise, fasting or extremes of temperature. In some cases, the acylcarnitine profile is helpful in diagnosis but, as with most FAO disorders, definitive diagnosis requires skin biopsy for fibroblast FAO flux studies. In about 20% of cases muscle biopsy shows lipid storage.

Patients with CPTII deficiency have poor exercise tolerance. Sometimes this can be improved by providing alternative energy sources that do not require CPT to get into the mitochondria. Carbohydrate-rich foods and drinks can be used before and during exercise. Medium-chain triglyceride (MCT) supplements, which can diffuse across the mitochondrial membrane, can be given as an alternative substrate for the β-oxidation pathway.

Very long-chain acylCoA dehydrogenase deficiency

Very long-chain acylCoA dehydrogenase deficiency (VLCAD) catalyses the first step in the β-oxidation of long-chain fatty acids. The late onset form of this disease is clinically indistinguishable from CPTII deficiency, although many patients are prone to cardiomyopathy and dysrhythmia. In VLCAD, the blood acylcarnitine profile is abnormal with an increased $C_{14:1}$ ratio. The diagnosis can be confirmed by fibroblast FAO studies. Treatment is the same as for CPTII deficiency.

Other β-oxidation pathway defects

Medium-chain acyl-Co A dehydrogenase deficiency (MCADD) is the most common FAO defect with an incidence of 1/10,000 live births. It ususally presents with hypoglycaemic hypoketotic encephalopathy towards the end of the first and into the second year of life. Because a significant number of affected infants either die or have significant cerebral damage in this first episode, neonatal screening is now widely available. Rare patients will present for the first time in adulthood with rhabdomyolysis or cardiomyopathy. Treatment is simple and effective: avoid prolonged fasts and use high carbohydrate intake during intercurrent illness. There is much debate as to the value of carnitine supplements in MCADD, but current UK practice is not to use them.

Multiple acyl-CoA dehydrogenase deficiency (MADD), also known as glutaric aciduria type II (GA-II), is caused by mutations in a number of different proteins that are involved in the mitochondrial transport of electrons from acyl-CoA to uniquinone. This results in a functional defect in a number of acyl-CoA dehydrogenases involved both in β-oxidation and in the degradation of branched-chain amino acids. The more severe forms lead to early death with non-ketotic hypoglycaemia and acidosis, but adult onset disease has also been described. This can involve metabolic decompensation, hypotonia, cardiomyopathy and rarely leucodystrophy with spastic quadriplegia. In milder cases, there is only a lipid storage myopathy and rhabdomyolysis. Biochemically, organic acids are detectable in the urine and there is a secondary carnitine deficiency.

The final stages of β-oxidation of long-chain fatty acids is catalysed by an enzyme complex termed the mitochondrial trifunctional protein (TFP). Mild TFP deficiency has a rather different phenotype to the other FAO defects. Patients present with progressive peripheral neuropathy. Exercise intolerance and episodic rhabdomyolysis may also occur.

Peroxisomal disorders

Peroxisomes are also involved in the oxidation of fatty acids, generally very long-chain fatty acids of 20 or more carbon lengths. The two most commonly encountered in adult practice are X-linked adrenoleucodystrophy or adrenomyeloneuropathy and Refsum's disease.

X-linked adrenoleucodystrophy (see Chapter 10)
Although the first clinical description of adrenoleucodystrophy (ALD) was reported over 90 years ago (known as Schilder's disease), our understanding of this disorder remains limited and therapy inadequate. The condition is inherited in an X-linked fashion with mutations found in *ALDP*, an ATP-binding cassette gene, located on Xq28, expressing a protein bound to peroxisomes. Currently, more than 500 different mutations have been recognized in affected families. The overall incidence in males varies between 1/20,000 and 1/40,000. The phenotypic expression is wide and varies between and within families. Classically, males present between 6 and 8 years with neurodegenerative ALD. This may or may not be associated with adrenal insufficiency which can occur in isolation. The typical adult disease presents with a spastic paraparesis in either males or females (AMN). Generally, females do not develop adrenal insufficiency nor the ALD phenotype. Twenty per cent of males with AMN may progress to adult onset ALD, which can rarely be the presenting feature. Finally, there are well-documented cases of asymptomatic carrier males living into their eighth decades. Although raised plasma very long-chain fatty acids are the hallmark of the condition, it is not entirely clear how they cause pathology. The neuropathology of ALD differs significantly from that of AMN: the former involves an inflammatory process, while the latter a 'dying back' phenomenon of axons. Very long-chain fatty acids can alter membrane properties and so be responsible for the axonopathy, but there is also evidence of an associated inflammatory process associated with demyelination with a perivascular lymphocytic infiltrate. Adrenal dysfunction is associated with abnormal cholesterol esters, adrenocortical atrophy and possible dysfunction of the adrenal adrenocorticotrophic hormone (ACTH) receptors.

Currently, therapy is inadequate. It is essential that adrenal replacement therapy is used if necessary. Treating the neurological manifestations is more problematic. Bone marrow therapy is at present the most effective intervention for cerebral forms in childhood, although it has to be used in the early stages of the disease and its mechanism of efficacy is not clear. Experience in adult onset ALD is extremely limited. Monitoring neuropsychometric status and MRI and/or MRS can be helpful in determining the timing of transplantation, but morbidity and mortality from the procedure is not inconsiderable. The other therapy that has been used over the past two decades is a low fat diet in combination with Lorenzo's oil (a 4 : 1 mixture of glyceryl trioleate and glyceryl trierucate). Unfortunately, no randomized controlled trial of this agent has been performed but recently presented data suggest that it can reduce the risk of disease progression in asymptomatic boys under 6 years of age from 77% to 23%. No good evidence exists for the efficacy of Lorenzo's oil in AMN. More recently, drugs used for other conditions – lovastatin and fenofibrate (hypolipidaemic agents) and sodium phenylbutyrate (used in urea cycle defects) – have been shown to reduce very long-chain fatty acid production *in vitro* by acting as peroxisomal proliferators. Early clinical studies sadly have been disappointing.

Refsum's disease
Refsum's disease is a rare inherited autosomal recessive neurodegenerative condition caused by a deficiency in phytanic acid α-hydroxylase. This leads to the accumulation of the fatty acid phytanic acid which is a neurotoxin. In affected individuals this is stored in neural and visceral parenchyma. The condition is characterized by retinitis pigmentosa, peripheral neuropathy, cerebellar ataxia and a high CSF protein without pleocytosis. The onset of symptoms ranged from childhood to the sixth decade. The condition may be precipitated or exacerbated by intercurrent infections and pregnancy. Progressive visual failure, often presenting as night blindness, results from a 'salt and pepper' retinitis pigmentosa and cataract formation. There may be cerebellar ataxia and a demyelinating sensorimotor polyneuropathy with symmetrical distal sensory impairment, and progressive mild to moderate distal weakness. Cardiac involvement may result in tachycardia, gallop rhythm, systolic murmur and cardiomegaly and the ECG shows non-specific ST changes. Other characteristic features include icthyosis which may be generalized or confined to the palms of the hands, anosmia, sensorineural deafness and epiphysial dysplasia characterized by syndactyly, pes cavus and hammer toes and hypoplasia of the limbs. The diagnosis is

Table 18.24 Other inborn errors of metabolism.

Defects in cholesterol and lipoprotein metabolism
- Hyperlipoproteinaemias
- Hypolipoproteinaemia
  - Hypobetalipoproteinaemia
  - Abetalipoproteinaemia
  - Tangier disease (familial high-density lipoprotein deficiency)

Disorders of nucleotide metabolism
- Defects in purine nucleotide metabolism
  - Lesch–Nyhan syndrome
  - Severe combined immunodeficiency disease
- Defects in pyrimidine nucleotide metabolism
  - Type I & II orotic aciduria
  - Ornithine transcarbamoylase deficiency

Disorders of copper metabolism
- Wilson's disease
- Menke's disease
- Haemochromatosis

Disorders of peroxisomes
- Zellweger's syndrome
- Neonatal adrenoleucodystrophy

Disorders associated with defective DNA repair mechanisms
- Ataxia telangectasia
- Xeroderma pigmentosum
- Cockayne's syndrome
- Fanconi's anaemia

established by finding elevated phytanic acid. The CSF shows a high protein but no pleocytosis. Postmortem examination may show widespread abnormal lipid storage in neural and visceral tissue including liver, heart and kidneys. The condition is exacerbated by the dietary intake of phytol and phytanic acid from beef and milk but the intake of chlorophyll-containing vegetables is safe because this cannot be broken down in the human gastrointestinal tract. The dietary intake of phytanic acid and phytol must be severely restricted for these patients.

Other inborn errors of metabolism

For other inborn errors of metabolism see Table 18.24.

Acknowledgement

Dr Kaustuv Bhattacharya, Clinical Research Fellow, Charles Dent Metabolic Unit, National Hospital for Neurology & Neurosurgery contributed to the section on Inborn Errors of Metabolism. The authors are most grateful for his help.

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19 Disorders of Consciousness, Intensive Care Neurology and Sleep

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Consciousness is a state of awareness of self and environment that gives significance to stimuli from the internal and external environment. It depends on two critical components – arousal or alertness and the cognitive content of mental functions – that allow awareness of self and environment and the expression of psychological functions of sensation, emotion and thought. Impairment of arousal leads to obtundation, stupor or coma, and a secondary impairment of cognitive content which may be temporary or permanent depending on the aetiology.

The anatomical substrate of coma consist of 'content', subserved by the cerebral hemispheres, and 'arousal' reflecting the integrity of the reticular activating system. Thus, coma can be caused either by bilateral hemispheric damage, or by a structural or metabolic lesion in the brainstem reticular activating system. Unilateral dysfunction of the cerebral hemispheres does not, by itself, cause stupor or coma. Neuro-anatomical studies of brainstem stroke confirm that the development of coma is associated with predominantly bilateral tegmental lesions of the upper pons and, to a lesser extent, the midbrain.

States of impaired consciousness

Neurologists are frequently asked to assess the level of consciousness of a patient to guide prognosis and likely outcome. The different patterns of arousal and awareness are complex and variable, but characteristic features allow recognition and classification of a spectrum of states of conscious level. These range from full consciousness to coma. Although a number of terms have been applied to these intermediate states, overlap inevitably occurs (Table 19.1).

Locked-in syndrome is not characterized by impaired consciousness but is included because it commonly presents diagnostic difficulties. It refers to a de-efferented state in which consciousness and cognition are preserved, but where the patient has lost motor function making movement and speech impossible. Horizontal eye movements are lost and the subject is usually able to communicate by opening and voluntarily moving their eyes in the vertical plane.

Causes of coma

Coma is caused by a large number of neurological and general medical disorders. In clinical practice, it is useful to classify the causes using a simple scheme. The most effective of these is to identify the following in the initial assessment of the patient (Table 19.2):

1 Presence of lateralizing signs;
2 Presence of meningism;
3 Pattern of brainstem reflexes.

The clinical assessment of coma is summarized in Table 19.3. Acute initial management includes cardiopulmonary resuscitation to ensure adequate oxygenation and airway protection; this involves tracheal intubation and mechanical ventilation when indicated. Intravenous access and maintenance of an appropriate arterial blood pressure should be provided by the use of intravenous fluids and/or inotropic drugs. During resuscitation, urgent determination of blood levels of glucose, electrolytes, renal and hepatic function, and a full blood count should be performed. Following this, in cases where the cause of coma is not apparent, 25 mL 50% glucose should be given intravenously; if alcoholism or malnutrition is suspected thiamine should be administered to prevent the development of Wernicke's encephalopathy. Naloxone or flumazenil should be administered if narcotic or benzodiazepine overdose is suspected. Further acute management of the unconscious patient includes adequate treatment of seizures, correction of electrolyte and acid–base disturbances and supportive treatment including adequate nutrition, nursing and physiotherapy.

Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

Table 19.1 Definitions and descriptions of states of altered consciousness.

Clouding of consciousness	States of reduced wakefulness characterized by impaired attention and memory. Patients may be distractible, hyperexcitable and irritable, with slow thought processes
Acute confusional state	Impairment of consciousness in which stimuli are intermittently misinterpreted. Patients are drowsy, bewildered, disorientated in time, and have poor short-term memory and comprehension. They may have difficulty undertaking complex tasks and show day–night reversal
Delirium	Rapid onset of a floridly abnormal mental state, with disturbed consciousness, disorientation, severe motor restlessness, fear, irritability, consistent misperception of sensory stimuli and visual hallucinations. There may be lucid periods with hyperactivity during which the patient is agitated, talkative and irritable. There are also hypoactive periods with hypersomnolence and sleep–wake inversion
Obtundation	Mental blunting with apathy and inactivity. The patient is drowsy with reduced alertness with a lessened interest in the environment
Stupor	Similar to deep sleep, from which the patient can be aroused only by vigorous and repeated stimuli. Even when aroused communication is by monosyllabic sounds and simple behaviours, and as soon as the stimulus ceases the stuporose subject lapses back into an unresponsive state
Akinetic mutism	Slowed or virtually absent bodily movements in the absence of paralysis or weakness. The patient is flaccid, does not respond to pain and lies immobile, mute and unresponsive to commands, questions and greetings. Wakefulness, alertness, sleep–wake cycles and self-awareness are preserved
Coma	A state of unrousable unresponsiveness in which the subject lies with eyes closed. There is no understandable response to external stimuli or inner need and the patient does not utter understandable responses nor accurately localizes noxious stimuli. Thus, there is a total absence of awareness of self and environment even when the subject is externally stimulated. There is no spontaneous eye opening, response to voice, localization to painful stimuli or verbal output

Table 19.2 (a) Causes of coma with intact brainstem function, without meningism and without lateralizing signs.

Toxins	Carbon monoxide, methanol, lead, cyanide, thallium, others
Alcohol	
Drugs	All sedatives, anaesthetics and many drugs, e.g. barbiturates, tranquillizers, opioids, psychotropics, salicylates, amphetamines, others
Extrapyramidal	Acute movement disorders (*status dystonicus*), neuroleptic malignant syndrome, serotonin syndrome
Seizures, epilepsy, etc.	Convulsive *status epilepticus*, non-convulsive *status epilepticus*, post-ictal, post-ictal (drug induced), non-epileptic *status*
Psychiatric	Catatonia, conversion reaction, malingering
Anoxic-ischaemic encephalopathy	
Respiratory	Hypoxaemia, hypercarbia
Electrolyte disturbances	Hyponatraemia, hypernatraemia; hypocalcaemia, hypercalcaemia; hypermagnesaemia
Diabetes mellitus	Hypoglycaemia, ketoacidosis, lactic acidosis, hyperosmolar non-ketotic diabetic coma
Uraemia/dialysis	
Hepatic encephalopathy	
Endocrine	Hypopituitarism, hypothyroidism, hyperthyroidism, hypoadrenalism, Hashimoto's encephalopathy
Core temperature change	Hypothermia, hyperpyrexia
Nutritional	Wernicke's encephalopathy
Inborn errors of metabolism	Hyperammoniacal states, aminoacidurias, organic acidurias
Others	e.g. porphyria, Reye's syndrome (hepatic), idiopathic recurrent stupor, mitochondrial disease, hypothalamic lesions, septic encephalopathy, malaria

Table 19.2 (b) Typical causes of coma with meningism (+/– intact brainstem function and +/– lateralizing signs).

Infection	Meningitis, encephalitis, malaria, HIV-related
Vascular	Subarachnoid haemorrhage (spontaneous or traumatic)

Table 19.2 (c) Typical causes of coma with intact brainstem function and asymmetrical lateralizing signs

Vascular
- Infarction
  - Ischaemia
  - Embolic – cardiac, large vessel, fat
  - Hypoperfusion/hypotension
- Haemorrhage
  - Extradural
  - Subdural
  - Subarachnoid
  - Intracerebral (primary or secondary)
  - Congophilic amyloid angiopathy
  - Intravascular lymphoma
- Vasculitis
- Venous thrombosis
- Mitochondrial disease
- Hypertensive encephalopathy
- Eclampsia
- Endocarditis
  - Bacterial, Libman–Sacks, marantic

Traumatic brain injury

Infection
- Brain abscess and tuberculoma, single or multiple
- Subdural empyema
- Creutzfeldt–Jakob disease
- Malaria, HIV-related

Brain neoplasms

White matter diseases
- Multiple sclerosis
- Leucoencephalopathy associated with chemotherapy and/or radiotherapy
- Acute disseminated encephalomyelitis
- Acute haemorrhagic leucoencephalitis
- Posterior reversible leucoencephalopathy
- Toxic leucoencephalopathy
- Progressive multifocal leucoencephalopathy

Table 19.2 (d) Causes of coma with intact brainstem function and symmetrical lateralizing signs (and see Table 19.2C)

Diffuse axonal (traumatic) brain injury
Bilateral subdural haematoma/empyema
Vascular
- Multiple infarcts due to:
  - Fat emboli
  - Cholesterol emboli
  - Disseminated intravascular coagulation
  - Thrombotic thrombocytopenic purpura
- Vasculitis

Table 19.2 (e) Causes of coma with signs of focal brainstem dysfunction

Herniation syndromes
Intrinsic brainstem disease
Advanced metabolic/toxic encephalopathy
Others
- Central pontine myelinolysis,
- multiple sclerosis, brainstem encephalitis

Vascular
- Vertebrobasilar occlusion, dissection, haemorrhage, AVMs

Mass lesions
- Posterior fossa tumours, abscesses, tuberculomas

Traumatic brain injury

Table 19.3 The comatose patient: immediate actions & assessment

1 Resuscitation and emergency treatment

2 Medical assessment

3 Establish level of consciousness
- Eye opening
- Motor responses
- Verbal output

4 Identify brainstem activity/brainstem reflexes
- Pupils
- Eye movements
  - Spontaneous
  - Oculocephalic
  - Oculovestibular
- Corneal reflexes and facial movements
- Bulbar
  - Cough
  - Gag
- Respiratory pattern

5 Motor function
- Involuntary movements
- Seizures
- Muscle tone
- Motor responses
- Tendon reflexes
- Plantar responses

Assessment of coma

Medical assessment

It is essential to obtain as detailed and accurate a history as possible of the acute event from all witnesses and to establish any history of a predisposing event, e.g. previous trauma, pyrexia, prodromal symptoms such as headache, neck stiffness, ataxia, epilepsy or previous episodes, medication list and psychiatric history (Table 19.3).

Examination

An urgent and detailed general medical examination must be undertaken immediately after resuscitation. The breath may smell of alcohol, ketones, hepatic or renal fetor. Examination of the mucous membranes may show evidence of cyanosis, anaemia, jaundice or carbon monoxide intoxication. Bruising in the mastoid or orbital regions or blood in the external auditory meatus may suggest temporal, orbital or basal skull fractures. Endocarditis is suggested by splinter haemorrhages, and opiate intoxication by hypodermic needle marks. Other relevant skin lesions include a purpuric petechial rash suggesting meningococcal septicaemia or a coagulation disorder, maculopapular lesions indicating viral meningo-encephalitis, endocarditis or fungal infection, or bullous lesions suggesting barbiturate intoxication.

Pyrexia is usually caused by systemic sepsis but its absence does not exclude infection, particularly in elderly or immunocompromised patients. Hyperpyrexia occurs in thyrotoxic crisis, heat stroke, drug toxicity and malignant hyperthermia. Primary neurogenic hyperpyrexia is unusual but can be associated with hypothalamic lesions or subarachnoid haemorrhage. Rarely, severe hypothermia may be the primary cause of coma, but more commonly hypothermia occurs as a result of coma from environmental (accidental hypothermia) or metabolic causes, endocrine disorders (hypothyroidism, hypopituitarism or hypoadrenalism) or drugs (e.g. alcohol, barbiturates).

Hypertensive crisis leads to disturbed consciousness, but hypertension is more commonly secondary to cerebral causes such as subarachnoid haemorrhage and raised intracranial pressure. Hypotension, resulting in coma, may be caused by hypovolaemia, myocardial infarction, septicaemia or diabetes mellitus.

The presence of meningism suggests infective or carcinomatous meningitis, subarachnoid haemorrhage or herniation (either central, tentorial or cerebellar tonsillar). The assessment of meningism is difficult in patients who have had tracheal intubation and meningism is unusual in deep coma whatever its cause. The pattern of respiration is of some localizing value (see below), but is also affected by cerebral herniation syndromes, metabolic and toxic conditions including drug overdose, acidosis, diabetes and liver disease.

Fundal examination may show retinopathy brought about by diabetes or hypertension. Papilloedema suggests raised intracranial pressure, hypertensive retinopathy or carbon dioxide retention and subhyaloid haemorrhage indicates subarachnoid haemorrhage. Otoscopic examination may reveal otorrhoea or haemotympanum from a basal skull fracture. Cerebrospinal fluid (CSF) rhinorrhoea can be confirmed by the presence of glucose in a watery nasal discharge but testing for 'beta-trace protein' is more specific.

Level of consciousness

The level of consciousness should be assessed by the ability of the patient to respond to stimuli of varying intensity by speech, eye opening and motor movements. Because of the importance of correctly identifying locked-in patients, the eyelids should be held open and the patient asked to move their eyes in a horizontal and vertical plane. Visual, auditory and painful stimuli of increasing intensity can then be systematically presented bilaterally in cranial nerve and limb territories.

Glasgow Coma Scale

The Glasgow Coma Score (GCS) is the most widely used (and reproducible) scale to assess the level of consciousness. It is a standard scoring system used for the assessment of the unconscious patient based on their motor, verbal and eye opening responses to external stimuli (Table 19.4). It was designed as an easily used, objective, reproducible scale for patients with head trauma, to assess varying levels of consciousness facilitating the early recognition of deterioration resulting from raised intracranial pressure, usually from herniation. It has proved an extremely valuable and durable scale which can easily be used by medical, nursing and paramedical staff. It requires regular and serial observations.

Table 19.4 Glasgow Coma Score (GCS).

Eye opening		Motor response		Verbal	
4	Spontaneous	6	Obeys command	5	Orientated
3	To speech	5	Localizes pain	4	Confused speech
2	To pain	4	Withdrawal	3	Inappropriate words
1	None	3	Flexion posturing	2	Incomprehensible sounds
		2	Extensor posturing	1	None
		1	None		

Table 19.5 FOUR score (Full Outline of UnResponsiveness).

Eye response	4	Eyelids open, tracking or blinking to command
	3	Eyelids open but not tracking
	2	Eyelids closed but open to a loud voice
	1	Eyelids closed but open to pain
	0	Eyelids remain closed with pain
Motor response	4	Thumbs-up, fist or peace sign
	3	Localizing to pain
	2	Flexion response to pain
	1	No response to pain or generalized myoclonic status
Brainstem reflexes	4	Pupil and corneal reflexes present
	3	One pupil wide and fixed
	2	Pupil or corneal reflexes absent
	1	Absent pupil, corneal and cough reflex
Respiration	4	Not intubated, regular breathing pattern
	3	Not intubated, Cheyne–Stokes breathing pattern
	2	Not intubated, irregular breathing pattern
	1	Breaths above ventilator rate
	0	Breaths at ventilator rate or apnoea

However, there are several limitations to its use. The scale excludes assessment of many important neurological functions, requires regular and consecutive observations to be effective, and is limited to the best response in a single limb. It therefore cannot represent asymmetry and has very poor diagnostic value. Its inter-rater reliability in non-experienced observers is also unreliable, not least because it is difficult to standardize the intensity of maximal auditory, visual and painful stimuli; full assessment cannot be undertaken in intubated patients or when soft tissue swelling prevents eye opening. Furthermore, the scale represents the addition of ordinal values that are not equal and are not independent of each other and it is relatively insensitive to changes in the level of consciousness at higher levels. Although the GCS score is helpful when assessing any change in the level of consciousness, particularly in the context of traumatic brain injury, it cannot replace detailed and careful neurological examination of the pattern of responsiveness.

A new coma score, the Full Outline of UnResponsiveness (FOUR) has been developed by Wijdicks *et al.* (2005) to overcome many of the difficulties inherent in the GCS (Table 19.5). Instead of the verbal component, the FOUR score includes pupil reactions and respiratory pattern to reflect brainstem function, thus making it more applicable in the intubated patient. The score provides greater neurological detail than the GCS and it has good inter-observer reliability.

Assessment of neurological function

Eyelids

In the patient in coma, opening of the eyelids by an examiner is followed by slow spontaneous re-closure while, in psychogenic coma, there is usually forceful resistance to eyelid opening and active closure. Rarely, the eyelids may be open in coma ('eyes open coma') because of a failure of inhibition of levator palpebrae associated with lesions in the ponto-mesencephalic region. In this situation, it is difficult to distinguish coma from the vegetative state.

Pupillary responses

In clinical practice, when assessing pupillary responses, it is essential to ensure an adequate light source and, if necessary, to examine the pupils with a magnifying glass. Pre-existing ocular or neurological injury, or topical or systemic medication, may cause pupillary asymmetry or even a fixed dilated pupil (Chapter 13).

The pupillary response indicates the functional state of the afferent (II) and efferent (III) pathways and the midbrain tegmentum. The presence of equal, light-reactive pupils indicates that the reflex pathway is intact. A normal pupillary reaction to light in a comatose patient suggests a metabolic rather than structural cause of the coma. Unilateral or bilaterally small pupils with normal reactions to light may be caused by Horner's syndrome associated with lesions involving the descending sympathetic pathways in the hypothalamus, midbrain, medulla (e.g. lateral medullary infarction) and ventrolateral cervical spine (e.g. cervical carotid artery damage). Bilateral pinpoint pupils with preserved light reflexes also occur with pontine lesions in the tegmentum that interrupt the descending sympathetic pathways. The extent of constriction makes it difficult to observe responses to light and magnification may be required. Mid position pupils, which do not respond to light but in which the accommodation reflex is spared, are associated with dorsal tectal, pretectal or tegmental lesions. The pupils may spontaneously and rhythmically fluctuate in size (hippus) and dilate to the ciliospinal reflex.

In progressive compressive IIIrd nerve lesions, the initial sign is a sluggish pupillary response followed by the development of fixed dilatation (caused by involvement of the parasympathetic with sparing of the sympathetic pathways). A unilateral IIIrd nerve lesion may also cause an efferent pupillary defect in which a light stimulus elicits a consensual but not a direct response. Widely dilated pupils caused by anticholinergic agents do not reverse with pilocarpine. Irregular oval, unequal pupils follow brainstem transtentorial herniation which leads to midbrain infarction. Fixed and moderately dilated pupils are seen in brain death because of the loss of both sympathetic and parasympathetic influences.

Oculomotor disorders

The preservation of normal eye movements means the entire brainstem is intact – from the oculomotor nucleus rostrally to the vestibular nuclei caudally, and their cerebellar conections (Chapter 13). In the primary ocular position, the eyes may be either dysconjugate, conjugate in the midline or deviated in a conjugate manner. Dysconjugate deviation of the eyes is common in patients with impaired consciousness and often reflects loss of descending voluntary control and may represent decompensation of a pre-existing strabismus or a cranial nerve palsy.

A complete IIIrd nerve palsy is manifest as pupillary dilatation, ptosis and deviation of the eye downward and laterally.

Oculomotor nerve palsies may occur as a consequence of midbrain lesions from direct trauma or as a manifestation of transtentorial herniation but have many other causes.

Internuclear ophthalmoplegia (INO), caused by a lesion of the medial longitudinal fasciculus, causes isolated failure of ocular adduction with nystagmus of the abducting eye but normal vertical eye movements and pupils. Dysconjugate vertical gaze may be caused by IVth nerve palsy which occurs commonly following trauma, metabolic encephalopathy or drug intoxication or a skew deviation associated with otolithic, cerebellar or brainstem lesions. Inward deviation and failure of abduction indicates a VIth nerve palsy which is common and may be caused by trauma or raised intracranial pressure but is a poor guide to localization. Tonic horizontal conjugate ocular deviation is common in coma. The eyes usually deviate towards the side of a destructive hemispheric lesion and away from the hemiparesis (e.g. infarction, haemorrhage or tumour). However, the eyes may deviate away from an irritative epileptic focus or from a thalamic lesion. Below the ponto-mesencephalic junction the eyes deviate away from the lesion side, and look towards the hemiparesis (pontine gaze palsy). In hemispheric lesions it is usually possible to drive the eyes across the midline with a vestibular stimulus but this is not true for brainstem gaze palsies. Seizure activity may cause intermittent aversive horizontal deviation although the eyes may deviate to the side of the focus in post-ictal gaze palsy. Tonic downward deviation of the eyes is associated with tectal compression caused by thalamic or dorsal midbrain lesions (usually haemorrhagic) but can be seen in metabolic coma or rarely in pseudocoma. Prolonged tonic upward deviation occurs as a consequence of extensive hypoxic-ischaemic damage but may occur transiently in seizures or in oculogyric crises caused by encephalitis lethargica or neuroleptic medication.

Horizontal nystagmus occurring in comatose patients suggests an irritative or a supratentorial aversive epileptic focus, usually associated with other motor manifestations of seizures including movements of the eyelids, face, jaw or tongue. Intermittent unilateral nystagmoid jerks in a horizontal or rotatory fashion indicate mid or lower pontine damage. Parinaud's syndrome (dorsal midbrain syndrome) is characterized by loss of upgaze, light-near dissociation of pupillary responses, convergence-retraction nystagmus and eyelid retraction (Collier's sign). There may also be accommodation or convergence spasm, associated oculomotor palsy (III, IV), skew deviation or internuclear ophthalmoplegia. It is associated with direct compressive lesions in the dorsal midbrain including pineal tumours, obstructive hydrocephalus, mesencephalic haemorrhage, arteriovenous malformation, trauma or multiple sclerosis (MS).

Spontaneous eye movements

Spontaneous roving eye movements

These are often intermittent slow random purposeless lateral movements, either conjugate or dysconjugate. This is a useful finding. Roving eye movements imply intact oculomotor brainstem pathways and point to a light coma, typically resulting from metabolic or toxic causes. Periodic alternating gaze disturbance is characterized by a slow cycle of horizontal gaze deviation in which the eyes are deviated for several minutes before moving to the opposite lateral gaze. This occurs in metabolic coma, particularly hepatic encephalopathy, but can also occur with bilateral hemispheric infarction or diffuse brain injury.

Conjugate vertical eye movements

These are separated into different types according to the relative velocities of the downward and upward phases (Table 19.6).

Repetitive rapid downbeat saccades, followed by slow movement back to the midline (ocular bobbing), are associated with intrinsic pontine or cerebellar lesions and metabolic or toxic coma. In ocular dipping there is an initial slow downbeat phase followed by a rapidly correcting saccade, this has less localizing value but may be associated with hypoxic-ischaemic injury. Rarely, the eye movements may be upwards in which the initial movement may be a rapid saccade followed by slow refixation (reverse ocular bobbing) or a slow initial upgaze phase followed by a corrective saccade (reverse ocular dipping). These movements are of little value in localization but may be associated with hypoxic-ischaemic coma or toxic and/or metabolic encephalopathy. Vertical nystagmus differs from ocular bobbing because there is no latency between the corrective saccade and the next slow deviation. Upbeat nystagmus is associated with disorders at the ponto-mesencephalic or ponto-medullary junction. In the primary position there is a slow downward drift followed by a rapid correcting saccade. Opsoclonus is characterized by intermittent bursts of large amplitude, rapid velocity and multidirectional saccades. It may occur as a paraneoplastic phenomenon or in viral encephalitis, metabolic encephalopathy or because of drug toxicity. If the movements are entirely horizontal they are called ocular flutter. Downbeat nystagmus (ocular myoclonus) in the primary position has an upward slow drift followed by a rapid downward saccade. It may have a rotatory or circular component and moves with the same frequency as palatal myoclonus. It is distinguished from ocular bobbing as there is no latency between the upward phase and the following downward jerk. It is associated with impairment of the lower brainstem in the region of the inferior olive and is particularly seen with the Arnold–Chiari malformation.

Vestibulo-ocular reflexes

Vestibulo-ocular reflexes (VOR) are the involuntary ocular movements that occur after stimulation of the vestibular apparatus, and can be tested either by mechanical rotation of the head (oculo-cephalic) or caloric irrigation (oculo-vestibular). If supranuclear influences are absent the eyes will normally remain fixed in space (i.e. continue to look forward). The oculo-cephalic reflex is tested by sudden passive rotation of the head in either lateral direction, or flexion and extension of the neck, while observing the motion of the eyes (Table 19.7). The manoeuvre should not

Table 19.6 Involuntary vertical eye movements in coma.

Ocular bobbing	Acute pontine lesion Metabolic and toxic Extra-axial posterior fossa masses	Rapid downward jerks of both eyes followed by a slow return to the mid position Paralysis of both reflex and spontaneous horizontal eye movements
Reverse ocular bobbing	Non-localizing Metabolic Viral encephalitis Pontine haemorrhage	Rapid conjugate upward jerk followed by slow downward drift that carries the eyes past the midposition. Then eyes slowly return to mid position
Ocular dipping	Diffuse cerebral Anoxia Following status epilepticus	Slow initial downward phase is followed by a relatively rapid return to mid position
Reverse ocular dipping	Viral encephalitis Metabolic encephalopathy Pontine infarction	Slow initial upward phase followed by rapid downward saccade returning the eyes to the mid position
Opsoclonus	Viral encephalitis Metabolic encephalopathy Drug toxicity	Intermittent high-velocity multidirectional saccadic eye movements
Upbeat	Cerebrovascular disease Multiple sclerosis Brainstem infarct Wernicke's encephalopathy	Slow downward drift followed by a rapid correcting saccade

Table 19.7 Oculocephalic responses.

Passive head movement (by examiner)	Response	Cause
Horizontal movement	Eyes remain conjugate and maintain fixation (move in opposite direction to head)	Normal with reduced level of consciousness
	No movement in either eye	Low brainstem lesion Peripheral vestibular lesion Drugs, anaesthesia
	Eyes move appropriately in one direction but do not cross the midline in the other	Gaze palsy (unilateral lesion in pontine gaze centre) Pontine lesion
	One eye abducts but the other fails to adduct	IIIrd nerve palsy Internuclear ophthalmoplegia (lesion of the median longitudinal fasciculus)
	One eye adducts but the other fails to abduct	VIth nerve palsy
Vertical movement	Eyes remain conjugate and maintain fixation (move in direction opposite head movement)	Normal with reduced level of consciousness
	No movement in either eye	Low brainstem lesion Peripheral vestibular lesion Drugs, anaesthesia
	Only one eye moves	IIIrd neve palsy
	Loss of upward gaze	Pretectal or midbrain tegmental compression

Table 19.8 Oculo-vestibular responses.

Irrigation (by examiner)	Response	Cause
Cold water instilled into the right ear	Nystagmus with slow phase to right and fast phase to left	Normal
	No response	Obstructed ear canal, dead labyrinth Low brainstem lesion
	Tonic deviation towards stimulated side (slow phase to right, no fast phase)	Supratentorial lesion with intact pons Toxic/metabolic, drugs Structural lesion above brainstem
	Dysconjugate response	Brainstem lesion (usually in region of medial longitudinal fasciculus)
	Downbeat nystagmus	Horizontal gaze palsy
	Vertical eye deviation	Drug overdose
Warm water instilled into left ear after no response to cold	Slow phase to right, fast phase to left	Peripheral VIIIth nerve lesion Labyrinthine disorder on right

be performed on any patient in whom cervical instability is suspected. When the head is rotated, regardless of the axis, incomplete abduction suggests a VIth nerve palsy while impaired adduction suggests a IIIrd nerve palsy or an INO. Reduced or absent oculo-vestibular reflexes indicate severe intrinsic brainstem impairment (Table 19.8). They are tested by irrigation of the tympanic membrane with cold or warm water (30°C or 44°C, respectively). In the awake subject, cold water causes a slow conjugate deviation of the eyes towards the stimulated ear followed by a corrective saccade towards the midline. Warm water irrigation causes conjugate eye deviation with a slow phase away from the stimulated ear followed by a corrective saccadic phase towards the ear. Simultaneous bilateral warm water application causes a slow upward deviation while simultaneous bilateral cold water application results in slow downward deviation. As with the oculo-cephalic manoeuvre, impaired abduction suggests a VIth nerve palsy while impaired adduction is compatible with a IIIrd nerve lesion or INO. Limited oculo-vestibular movements may be caused by metabolic and/or toxic coma or drug intoxication. Vertical movements are impaired by disorders of the midbrain particularly affecting regions responsible for maintaining consciousness, while pontine lesions lead to loss of horizontal saccadic movements.

Other cranial nerves

The eyes are usually closed in coma. However, if the patient is in light coma and if both afferent and efferent limbs of the corneal reflex are intact and the eye is held open, a blink reflex can be elicited in response to corneal or eyelash stimulation. The blink reflex may be lost with a lesion at the level of the pons, interrupting the afferent pathway along the Vth cranial nerve but unilateral absence of blinking indicates a lesion of the VIIth nerve affecting the efferent pathway. In this situation the stimulus may induce deviation of the jaw to the opposite side (corneopterygoid reflex). The corneal reflex has a higher threshold in comatose patients but may be totally lost with deep sedation. The jaw jerk may be brisk and the presence of clonus suggests involvement of the corticobulbar tract or metabolic encephalopathy but it is also seen during weaning from sedation or in the vegetative state. In coma the facial grimace to painful stimuli reflects VIIth nerve function. Lesions at a pontine level may damage facial nerve nuclei and produce ipsilateral complete facial weakness. Upper motor neurone lesions produce contralateral facial weakness, but tend to spare the forehead and orbicularis oculi muscles because of the bilateral cortical representation.

Bulbar function

The clinical assessment of bulbar function in patients with an altered level of consciousness is difficult and unreliable. Airway protection may be impaired despite the presence of palatal movement and a pharyngeal and cough reflex. In an intubated patient the cough reflex may be tested indirectly by manipulating the tracheal tube or by administering tracheal suction. An impaired cough reflex is manifest as a poor or absent cough response, absence of distress and lack of lacrimation, and implies a central medullary lesion although the response may also be depressed by metabolic encephalopathy or by lesions of the afferent vagal pathway or efferent limb to the respiratory muscles. The pharyngeal (gag) reflex is also difficult to assess in comatose patients as it is suppressed by sedative drugs. However, impairment of palatal and uvula elevation upon pharyngeal and palatal stimulation implies low brainstem impairment.

Respiration

Several characteristic patterns of respiratory irregularity have been described but it is difficult to attribute precise respiratory function to discrete anatomical substrates because lesions are rarely localized and coexisting pulmonary, cardiovascular or autonomic influences may complicate the clinical picture. Furthermore, earlier recognition of respiratory insufficiency has led to rapid therapeutic intervention with controlled ventilation.

Primary central neurogenic hyperventilation is a rare condition characterized by rapid regular hyperventilation that persists in the face of alkalosis, elevated PaO_2, low $PaCO_2$ and in the absence of any pulmonary or airway disorder. However, in the critically ill patient, an increased respiratory rate in coma is more commonly secondary to intrinsic lung involvement, especially aspiration pneumonia.

Apneustic breathing consists of sustained inspiratory cramps with prolonged pauses at full inspiration or alternating brief end-inspiratory and expiratory pauses. The pattern has been associated with bilateral tegmental infarcts or demyelination in the pons (Figure 19.1).

In ataxic respiration there is a completely irregular respiratory cycle of variable frequency and tidal volume alternating with periods of apnoea; it is particularly associated with medullary impairment, either because of brainstem stroke or compression and it is important to recognize as it may herald impending respiratory arrest. Hiccups consist of brief bursts of intense inspiratory activity involving the diaphragm and inspiratory intercostal muscles.

Intractable hiccups may be the result of structural or functional disturbances of the medulla or its afferent or efferent connections with the respiratory muscles. The presence of hiccups in this context may also presage the development of respiratory arrhythmia culminating in respiratory arrest.

Voluntary control of breathing may be impaired by bilateral lesions affecting the descending cortico-spinal or cortico-bulbar tracts, and is particularly seen in association with destructive vascular lesions of the basal pons or of the medullary pyramids and adjacent ventromedial portion which may result in the 'locked-in' syndrome (Figure 19.2). Selective interruption of the voluntary pathways leads to a strikingly regular and unvarying respiratory pattern, with loss of the ability to take a deep breath, hold the breath, cough voluntarily or initiate any kind of volitional respiratory movement although the respiratory pattern may vary with emotional stimuli. These patients can often be weaned from artificial ventilation.

Cheyne–Stokes respiration (CSR) is characterized by a smooth waxing and waning of breath volume and frequency separated by periods of central apnoea. The respiratory oscillations are associated with phasic changes in cerebral blood flow, CSF pressure, arterial and alveolar O_2 and CO_2, level of alertness and pupillary size; periodic heart block and ventricular arrhythmias are also

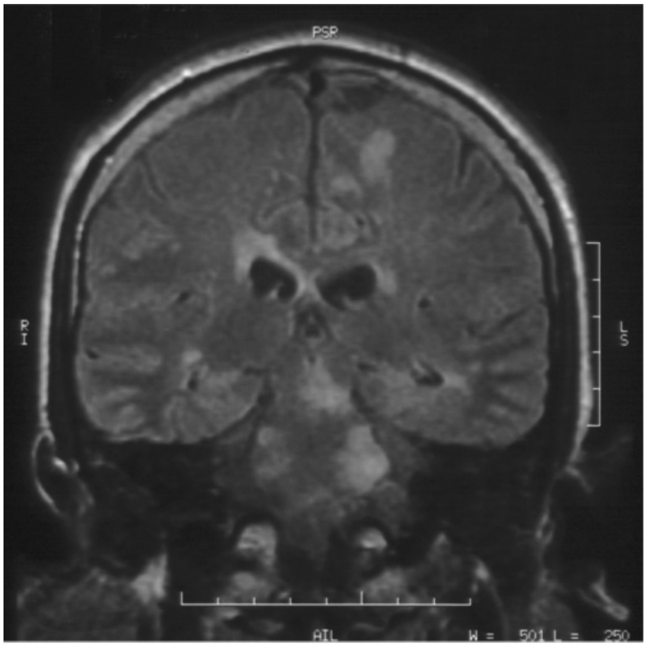


Figure 19.1 Extensive plaques of demyelination in a patient with progressive central apnoea requiring ventilatory support (MRI T1W).

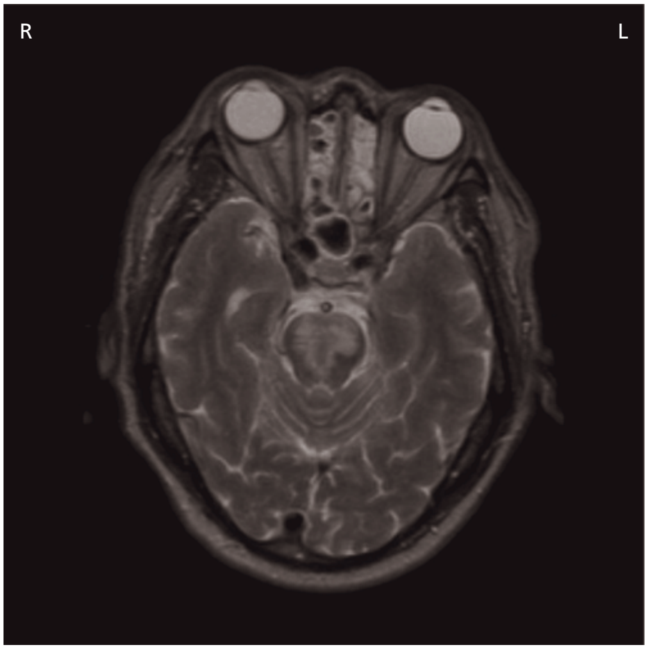


Figure 19.2 Extensive pontine infarction due to vertebrobasilar occlusion in a patient with locked-in syndrome (MRI T2W).

common. Neurogenic CSR is associated with diffuse metabolic encephalopathy, cerebrovascular disease and raised intracranial pressure and may occur with supratentorial or, less commonly, infratentorial structural lesions.

Motor responses

Examining the motor responses involves assessment of the resting posture of the limbs and head, involuntary movements, spontaneous movements (purposeful or non-purposeful) and the response to external stimuli. The motor response to deep painful stimuli is extremely valuable in assessing diagnosis and prognosis of coma.

First, the patient may lie in a fixed posture which is exacerbated by stimulation. Two characteristic patterns of generalized reponses are recognized. Decorticate posturing refers to flexion at the elbows and wrists with shoulder adduction and internal rotation and extension of the lower extremities. It has a poor localizing value and may result from lesions of the hemispheres or thalamus above the diencephalon. Decerebrate posture is characterized by bilateral extension of the lower extremities, adduction and internal rotation of the shoulders and extension at the elbows. It is usually caused by brainstem lesions, particularly of the bilateral midbrain or pons, and carries a poor prognosis. Occasionally, decerebrate posturing occurs as a result of severe metabolic encephalopathy (e.g. caused by hypoglycaemia or liver failure) or bilateral supratentorial lesions involving the motor pathways.

In clinical practice the pattern of motor response to stimuli is often mixed within the same patient with localizing, flexion or extension movements occurring in different limbs and varying with recovery. Severe hypoxic-ischaemic encephalopathy may cause extension and pronation of the upper extremities and forcible plantar flexion of the foot and intermittent opisthotonus induced by painful stimuli. Medullary lesions may be associated with total flaccidity, but lower limb clonus is occasionally seen.

Tone

The pattern and asymmetry of muscle tone may be helpful in localizing focal structural lesions, and may help in differentiating metabolic from structural coma. The presence of spasticity implies established lesions while acute structural damage above the brainstem or metabolic encephalopathy usually leads to hypotonia and flaccidity. The presence of a unilateral grasp reflex indicates an ipsilateral frontal lobe disturbance. Plucking or clutching movements of the limbs indicate light coma and intact cortico-spinal pathways.

Involuntary movements

Tonic–clonic or other stereotyped movements suggest generalized or focal seizures or epilepsia partialis continuans. Myoclonic jerking (non-rhythmic jerking movements in single or multiple muscle groups) is seen with hypoxic-ischaemic encephalopathy, metabolic coma (e.g. hepatic encephalopathy) or, occasionally, following pontine infarction. Rhythmic myoclonus must be distinguished from *epilepsia partialis continua*. Myoclonic seizures typically lack a tonic component and may involve facial muscles and other axial structures. Stimulus-sensitive myoclonus may be precipitated by touch, tracheal suction or loud hand clapping. Myoclonic status should be distinguished from other types of generalized seizures; it is seen in approximately 40% of survivors from post-anoxic coma immediately following resuscitation and is highly predictive of vegetative state or death. However, some patients who recover from post-anoxic coma develop late onset multifocal action and stimulus-sensitive myoclonus (Lance–Adams syndrome). This improves with time and is only rarely associated with persistent or severe additional neurological deficit. Occasionally, intermittent tonsillar herniation may cause cerebellar paroxysms characterized by a deterioration in the level of arousal, opsithotonus, respiratory rate slowing and irregularity, and pupillary dilatation.

Distinction of toxic and metabolic coma from structural coma

It is often possible to distinguish metabolic encephalopathy from structural causes on the basis of clinical examination although non-convulsive status epilepticus can resemble both causes. The preceding medical history may suggest a metabolic abnormality and the onset is more likely to be acute in the presence of a structural lesion. Metabolic or toxic lesions usually result in coma without lateralizing or brainstem signs while structural lesions may be suggested by asymmetrical motor signs. Metabolic encephalopathy is favoured by the presence of involuntary limb movements (tremor, myoclonus and asterixis), abnormalities of the respiratory pattern (hypoventilation or hyperventilation) and the presence of acid–base disturbances. The level of consciousness tends to fluctuate and be lighter in patients with metabolic disorders. However, these clinical features are merely indicators; structural lesions such as subarachnoid haemorrhage, cortical venous thrombosis, bilateral subdural haematoma or multifocal central nervous system disease (vasculitis, lymphoma, meningitis or haematoma) may present with bilateral symmetrical signs and metabolic disorders (e.g. hypoglycaemia) may present with focal signs.

Psychogenic unresponsiveness

This may be distinguished by history, examination and, if necessary, investigations. There are often atypical factors in the history and occasionally obvious psychiatric precipitating factors. Examination reveals inconsistent volitional responses, particularly on eyelid opening. Spontaneous saccadic eye movements are often present, and pupillary constriction will occur on eye opening. Oculo-vestibular stimulation with cold stimulus will show preservation of the fast phase away from the stimulated side. Finally, electroencephalography (EEG) will show responsive alpha rhythms.

Outcome from coma

Most patients who survive the initial insult recover from coma within 2–4 weeks, although the pattern and extent is highly variable, ranging from vegetative state to full recovery. It is not possible to assess the prognosis of a patient in coma with accuracy but a number of clinical factors help in predicting the likely outcome.

Aetiology

Coma associated with drug and alcohol ingestion or metabolic disturbance generally carries a good prognosis for recovery providing there is no severe underlying disorder. The prognosis for a patient in traumatic coma is better than that for a patient at a similar level of coma from non-traumatic causes. These patients are usually younger and continued improvement may occur despite prolonged coma and severe disability. Patients in coma caused by structural cerebral disease (e.g. cerebrovascular disease or subarachnoid haemorrhage) carry the poorest prognosis, with only 7% achieving moderate or good recovery. Outcome from coma following cardiac arrest, whether the event occurs ‘out of hospital’ or in a hospital setting with resuscitation facilities, is also poor; other important features indicating a poor prognosis in these patients include an unwitnessed arrest, failure to initiate immediate basic life support, asystole, prolonged arrest time and the administration of high doses of adrenaline (epinephrine).

Depth of coma

The depth of coma, as determined by GCS and by the presence or absence of reflexes in the cranial nerve territory, is a sensitive guide to outcome. The best outcome is associated with patients who maintain normal brainstem reflexes throughout resuscitation and in whom there is early recovery of speech, orientating spontaneous eye movements, oculo-cephalic reflexes, ability to follow commands and normal skeletal muscle tone. For example, the presence of eye opening, grunting and limb flexion to noxious stimuli within 3 hours of cardiopulmonary arrest is associated with a moderate or good recovery in up to 20% of patients.

Duration of coma

Survival following cardiorespiratory arrest is closely correlated with the duration of coma. Only 12% of patients comatose more than 6 hours after cardiac arrest survive with a good outcome or moderate deficits and, if there is no eye opening, vocal response or motor function after 6 hours the patient has only a 6% chance of making a moderate or good recovery. A good outcome is possible if the patient withdraws the arms to pain, localizes pain or follows simple one-step commands within 72 hours of the arrest. Awakening after more than 3 days of coma from anoxia is very frequently associated with severe disability. Non-traumatic coma lasting for more than 1 week is associated with only a 3% prospect of good recovery. The absence of brainstem reflexes and absent motor responses to pain and GCS < 5 for more than 3 days or <8 for more than 7 days all indicate an extremely poor prognosis for recovery of brainstem function.

Co-morbidity

There is a clear correlation between outcome and age at cardiac arrest. The presence of coexisting general medical disorders is also associated with a poor outcome. These include ischaemic heart disease, structural cardiac disease, hypertension, diabetes mellitus, impaired renal function and the presence of pneumonia or sepsis. Many patients have coexisting cardiac disease that limits their performance, and a significant proportion of patients who survive the initial event may still die suddenly in the first year. For out-of-hospital arrests, 10% of survivors died from cardiac complications alone. The presence of coexisting carotid stenosis may lead to a symmetrical global or watershed infarction.

Other factors

Myoclonic status carries a very poor prognosis. In a recent series of 107 comatose survivors of out-of-hospital arrest, 40 had generalized repetitive and often sound-sensitive myoclonus involving the limbs and face, trunk and diaphragm, often leading to impairment of mechanical ventilation and gas exchange. Comatose patients with myoclonic status frequently demonstrate burst-suppression or alpha coma patterns on EEG. Similarly, status epilepticus in post-anoxic coma is resistant to therapy and should be considered a marker of anoxic damage.

Prognostic value of investigations

Imaging findings are also important in determining prognosis. The presence of anteroseptal shift, extensive subcortical change (Figure 19.3), temporal lobe infarction and hydrocephalus imply a worse outlook. Intracranial pressure is also important as a prognostic determinant, particularly in traumatic coma. The finding of an iso-electric EEG, burst-suppression or ‘alpha coma’ (8–12 Hz rhythm, which is not localized to the occipital lobe, and which does not suppress upon eye opening) are all associated with a poor prognosis. Absent cortical somato-sensory evoked potentials performed >12–24 hours after cardiorespiratory arrest, in the absence of structural abnormalities or sedation indicate no chance for return of consciousness.

In summary, the most important predictive features for survival in patients in coma resulting from severe head injury for more than 6 hours are depth of coma as defined by the GCS (pupillary responses, eye movements and motor responses) and patient age. The extent of injury, the presence of skull fracture, hemispheric damage or extracranial injury are less important in determining survival and residual disability. Secondary insults such as raised intracranial pressure and low cerebral perfusion pressure are associated with an increase in severe disability and higher mortality.

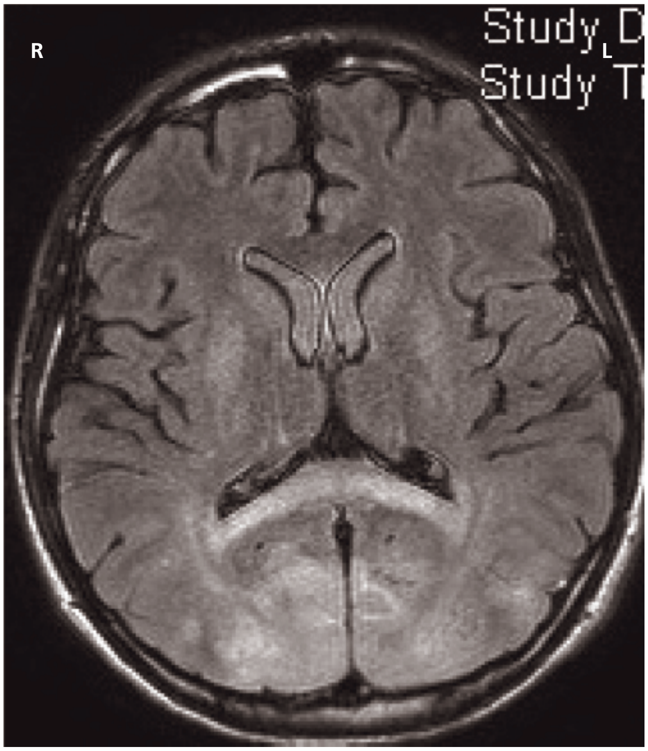


Figure 19.3 Global ischaemic-hypoxic brain lesions (T1-weighted axial MRI).

In non-traumatic coma, absent brainstem reflexes and motor responses at 24 hours indicate a poor prognosis but the combination of GCS at 48 hours, somatosensory evoked potential (SSEP) and EEG permits a more reliable prediction of outcome. The most accurate guide to a poor prognosis following a cardiorespiratory arrest is the absence of pupillary light reflexes, corneal reflexes and motor responses (except extensor plantar responses) at 3 days. Other factors may also indicate a poor outcome including the absence of other brainstem reflexes, GCS < 5, loss of cortical N20 response on short latency SSEPs at 1–3 days, elevated serum neurone-specific enolase level and an EEG showing alpha coma, burst suppression or an isoelectric trace. Computed tomography (CT) scan findings may also be important in determining prognosis. The presence of anteroseptal shift, temporal lobe infarction and hydrocephalus imply a worse outlook. When these abnormalities are seen at 3 days they provide adequate prognostic information to allow discussion with relatives about the patient's wishes and likely outcome. However, these indicators are not specific and so a poor outcome may also occur even if the initial signs suggest recovery. It must be emphasized that many of these findings relate to studies that were undertaken several years ago. It is likely that with better techniques of intensive care, physiological measurement and cerebral protection these data are less reliable and should therefore only be used as a general guide.

Vegetative state

Patients in a vegetative state appear to be awake with their eyes open but show no evidence of awareness of self or environment, are unable to interact with others and have no evidence of sustained reproducible purposeful or voluntary behavioural responses to visual, auditory, tactile or noxious stimuli. There is no evidence of language comprehension or expression. Patients are able to breathe spontaneously and the gag, cough, sucking and swallowing reflexes are usually present. Sleep–wake cycles are preserved as are hypothalamic and brainstem autonomic responses. There is bladder and bowel incontinence but cranial nerve (pupillary, vestibulo-ocular, corneal and gag), spinal and primitive reflexes are variably preserved. Inconsistent non-purposive movements, facial grimacing, smiling and frowning, chewing, swallowing, bruxism, vocalization, grasping and inconsistent auditory and oculomotor orientating reflexes to peripheral sounds or movement may occur. The diagnosis of vegetative state is not tenable if there is any degree of voluntary movement, sustained visual pursuit, consistent and reproducible visual fixation or response to threatening gestures.

The vegetative state usually develops after a variable period of coma; it may be partially or totally reversible or may progress to a persistent vegetative state or death. The persistent vegetative state is defined as a vegetative state that has continued for at least 1 month. This definition does not imply permanency or irreversibility. The term permanent vegetative state should be avoided for this reason.

Minimally conscious state

Patients in this state are no longer in coma and do not satisfy the description of vegetative state because they demonstrate low level behavioural responses consistent with severe neurological impairment and disability. This condition includes a wide variety of responses. Patients who are minimally responsive may be able to show consistent evidence of awareness of themselves or their environments by following simple commands, gestural or verbal yes/no responses, intelligible speech or purposeful behaviour. They are not able to communicate consistently. These patients may remain in minimally responsive states or eventually recover some ability to communicate reliably or use objects functionally.

Locked-in syndrome

The locked-in syndrome is characterized by preservation of consciousness with dissociation between automatic and volitional control of lower cranial nerve and limb function. Volitional respiratory, facial, bulbar and limb control is lost but there may be involuntary phenomena including ocular bobbing, facial grimacing, oral automatisms and trismus, palatal myoclonus and emotional responses including laughing and crying. There is preserved awareness of the environment and self, and patients can usually communicate through vertical eye movements, which are preserved with synergistic elevation of the upper eyelids when looking upwards. These vertical eye movements are often slow and incomplete, but are the only way in which the patient can communicate because there is usually a horizontal gaze palsy, anarthria and tetraplegia. Because these patients are not in coma it is important to establish a consistent form of communication, however laborious it may be for the carers.

The most frequent cause of locked-in syndrome is occlusion of the vertebro-basilar system, usually predominantly in the rostral or middle segments. Pontine haemorrhage or embolism may also cause the condition. Other causes of the syndrome have been described in which the lesion was situated in the ventral pontine tegmentum, basis pontis or in the mesencephalic region at the level of the cerebral peduncles. Cases of locked-in syndrome resulting from bilateral internal carotid artery lesions have also been described. The aetiology of non-vascular cases include central pontine myelinolysis, trauma, encephalitis, tumour, pontine abscess, MS and heroin abuse. Peripheral lesions (i.e. severe neuropathy such as Guillain–Barré syndrome) may cause an apparent locked-in syndrome with severe limb, facial and bulbar paresis, although respiration is frequently affected because of respiratory muscle involvement. In addition, vertical eye movements are not spared in the same way as with the classic syndrome.

Functional recovery is possible in both vascular and non-vascular groups of locked-in patients and therefore an aggressive rehabilitation programme should be instituted as early as possible to allow the patient to achieve the highest possible level of recovery as rapidly as possible. However, the prognosis for most patients in locked-in syndromes is poor, with severe residual disability. The mortality rate is high with most deaths occurring in the first 4 months, either from extension of the lesion or from respiratory complications (pneumonia, respiratory arrest or pulmonary embolus).

Determining brain death

Cardiac and respiratory function can be maintained artificially for prolonged periods after the brain has ceased to function. The diagnosis of brain death is necessary if the possibility of organ donation exists, and when withdrawal of artificial life support is considered. These are both delicate issues and must be approached with appropriate sensitivity.

Brain death is diagnosed in three stages. First, it must be established that the patient has suffered an event of known aetiology resulting in irreversible brain damage with apnoeic coma, i.e. the patient is deeply unconscious, mechanically ventilated with no spontaneous respiratory movement; secondly, reversible causes of coma must be excluded; and, thirdly, a set of bedside clinical tests of brainstem function are undertaken to confirm the diagnosis of brainstem death.

The procedure is as follows:

1 The cause of coma must be known to be from irremediable brain damage of known aetiology. This may be obvious within hours of a primary intracranial event such as a severe head injury, or spontaneous intracranial haemorrhage but diagnosis may be more difficult following hypoxic brain injury or encephalitis.

2 There should be no evidence that coma is caused by depressant drugs or neuromuscular blocking agents. Narcotics, hypnotics and tranquillizers may have prolonged action, particularly when hypothermia coexists or in the context of renal or hepatic failure. Determination of sedative drug levels and tests of neuromuscular function may be necessary.

3 Primary hypothermia (<35°C) as the cause of unconsciousness must have been excluded.

4 Potentially reversible circulatory, metabolic and endocrine disturbances must have been excluded as the cause of the continuation of unconsciousness.

5 The patient is being maintained on the ventilator because spontaneous respiration has been inadequate or has ceased.

6 All brainstem reflexes are absent:

- The pupils are fixed, dilated and do not respond to sharp changes in the intensity of light;
- There is no corneal reflex (care should be taken to avoid damage to the cornea because this may be harvested during organ donation);
- The vestibulo-ocular reflexes are absent. No eye movements are seen during or following the slow injection of at least 50 mL ice cold water over 1 minute into each external auditory meatus in turn. Wait several minutes before testing the other side. (Clear access to the tympanic membrane must be established by direct inspection and the head should be flexed at 30°);
- There is no gag reflex or reflex response to bronchial stimulation when a suction catheter is passed into the trachea;
- No motor responses can be elicited following painful stimulation applied to an area within the cranial nerve distribution;
- No respiratory movements occur when the patient is disconnected from the mechanical ventilator. During this test the $PaCO_2$ should reach 6.65 kPa. This should be ensured by arterial blood gas measurement. Hypoxaemia following disconnection from the ventilator should be prevented by pre-oxygenating the patient with 100% oxygen for 10 minutes while on the ventilator and then delivering oxygen at 6 L/minute through a catheter situated in the tracheal tube when mechanical ventilation is temporarily removed. This test is specifically examining the function of the respiratory centre;
- Clearly, there are many peripheral causes of ineffective respiration for which brainstem testing is completely inappropriate.

Repetition of testing

In the UK the diagnosis of death by brainstem testing should be made by at least two medical practitioners who have been registered for more than 5 years, have been trained in this field and are not members of the transplant team. The complete set of tests should always be performed on two separate occasions by the two practitioners working alone or together. The interval between tests has not been defined in adults, and usually the tests are repeated within a short period to avoid further distress to the patient's relatives. In legal terms, the time of death is taken as the time of the first failed brainstem test.

It is essential that relatives, partners and carers be kept fully informed of the clinical condition of the patient and that explanation be given to them regarding the condition and prognosis. They should be given explanation of the investigations being undertaken and of their interpretation throughout the process of the determination of death of the brainstem in a sympathetic, timely and appropriate fashion by those concerned with the management of the patient.

Neurological intensive care

Dedicated neurological intensive care units (NICUs) are predominantly involved with the management of primary encephalopathic patients, the control of raised intracranial pressure, the management of ventilatory, autonomic and bulbar insufficiency, and the consequences of profound neuromuscular weakness. The increasing availability of neurological intensive care in Europe and the USA has allowed a focus on all critical needs of the neurological patient as well as the management of peri-operative instability of patients with neurosurgical or interventional neuroradiology. In general, critical illness resulting from primary neurological diseases such as myasthenia gravis, Guillain–Barré syndrome, CNS infections, status epilepticus and stroke have a better outcome than those patients with neurological disease secondary to general medical disorders seen on general ICUs. However, such patients remain dependent on ICU support for very much longer periods of time. This results in very significant psychological demands on the patients, their carers, nurses, physicians and other health care professionals. However, there is sound evidence that patients with critical neurological disease have better outcomes when cared for in dedicated NICUs.

Indications for intensive care management of neurological patients

The major indications for considering admission to NICU are summarized in Table 19.9.

Table 19.9 Indications for admission to neurological intensive care unit (NICU).

- Impaired level of consciousness
- Impaired airway protection
- Progressive respiratory impairment or need for mechanical ventilation
- Seizures
- Clinical or CT evidence of raised ICP caused by space-occupying lesions, cerebral oedema or haemorrhagic conversion of a cerebral infarct
- General medical complications (e.g. hypertension or hypotension, aspiration pneumonia, sepsis, cardiac arrhythmias, pulmonary emboli)
- Monitoring (e.g. level of consciousness, respiration, ICP, EEG)
- Specific treatments (e.g. neurosurgical intervention, intravenous or arterial thrombolysis)

Ventilatory failure associated with neurological disease

The central and peripheral causes of ventilatory insufficiency or failure that may require admission to the NICU are listed in Tables 19.10 and 19.11.

It is essential to anticipate the development of respiratory failure before the emergence of hypoxia and/or hypercapnia. Thus, the threshold for tracheal intubation is lower in the context of rapidly progressive neuromuscular weakness. Patients with acute neurological disorders require tracheal intubation and ventilation because of the development of acute respiratory insufficiency or because they are unable to protect their upper airway from obstruction as a consequence of impaired consciousness or bulbar weakness. The latter predisposes to pulmonary aspiration of saliva and food that cannot be cleared by the patient because of an inadequate cough secondary to poor diaphragmatic and anterior abdominal wall musculature. Bronchopneumonia often results.

The most useful and reproducible bedside test of ventilatory function is the measurement of the forced vital capacity (FVC). The normal value is approximately 70–75 mL/kg. Serial measurements often indicate whether respiratory muscle function is stable or deteriorating and are especially important in fluctuating diseases such as myasthenia gravis. By the time arterial blood gas tensions have become abnormal respiratory muscle function is often severely compromised.

There are a number of indications for tracheal intubation and mechanical ventilation and these are listed in Table 19.12.

Neurological indications for tracheal intubation and mechanical ventilation

The nature of neurological respiratory failure can dictate a prolonged period of mechanical ventilation. When this is the case, the orotracheal tube should be replaced by a tracheostomy as soon as possible. Tracheostomy allows greater patient comfort, easier nursing management (including suction), and the possibility of oral nutrition and speech, as well as aiding weaning from mechanical ventilation by reducing respiratory dead space.

Mechanical ventilation

Mechanical ventilation of the lungs may be provided by intermittent negative pressure ventilation or intermittent positive pressure ventilation. The former is delivered using devices such as tank ventilators (iron lungs) and cuirass ventilators; apart from in a few specialized units, these devices are rarely used nowadays. Modes of ventilation are summarized in Table 19.13.

Table 19.10 Central causes of ventilatory insufficiency or failure that may require admission to a neurological intensive care unit (NICU).

Cortical
Epilepsy
Vascular
Tumour
Metabolic
Infection

Brainstem
Congenital (Ondine's curse) – primary alveolar hypoventilation
Tumour
Vascular
Multiple sclerosis and acute disseminated encephalomyelitis
Motor neurone disease
Infection:
  Borrelia
  Listeria
  Post varicella encephalomyelitis
  Poliomyelitis
  Encephalitis lethargica
  Western equine encephalitis
Paraneoplastic
Leigh's disease
Reye's syndrome
Hypoxaemia

Foramen magnum and upper cervical cord
Arnold–Chiari malformation – cerebellar ectopia
Achondroplasia, osteogenesis imperfecta
Rheumatoid arthritis – odontoid peg compression
Trauma
Vascular

Cervical and upper thoracic spinal cord
Acute epidural compression caused by neoplasm or infection
Acute transverse myelitis
Cord infarction
Other myelopathies (including traumatic)
Tetanus

Autonomic
Multi-system atrophy

Extrapyramidal
Status dystonicus

Table 19.11 Peripheral causes of ventilatory insufficiency or failure that may require admission to a neurological intensive care unit (NICU).

Anterior horn cell
Motor neurone disease
Poliomyelitis or post polio syndromes
Rabies

Multiple radiculopathies
Carcinomatous meningitis
AIDS polyradiculitis

Polyneuropathy
Acute inflammatory demyelinating polyneuropathy (AIDP)
Acute motor and sensory axonal neuropathy (AMSAN)
Acute motor axonal neuropathy (AMAN)
Critical illness polyneuropathy
Other polyneuropathies:
  Hereditary sensorimotor
  Acute porphyria
  Organophosphate poisoning
  Herpes zoster/varicella
  Neuralgic amyotrophy

Neuromuscular transmission defects
Myasthenia gravis
Lambert–Eaton myasthenic syndrome
Neuromuscular blocking agents
Other:
  Botulism
  Toxins
  Hypermagnesaemia
  Organophosphate poisoning

Muscle
Dystrophy
  Duchenne, Becker, limb girdle, Emery–Dreyfuss
Inflammatory
Myotonic dystrophy
Metabolic
  Acid maltase deficiency
Mitochondrial myopathies
Myopathies associated with neuromuscular blocking agents and steroids
  Acute quadriplegic myopathy
Myopathy and sepsis
Cachectic myopathy
HIV-related myopathy
Sarcoid myopathy
Hypokalaemic myopathy
Rhabdomyolysis
Periodic paralysis

Table 19.12 Indications for tracheal intubation.

- A decreasing forced vital capacity in the presence of bulbar dysfunction
- Impending neuromuscular respiratory failure (forced vital capacity <20 mL/kg, tachypnoea, poor cough, dyspnoea at rest, use of accessory muscles, staccato speech)
- Respiratory failure ($PaO_2 < 8$ kPa (60 mmHg) breathing room air) with or without hypercarbia
- Inability to protect airway
- Failure of central regulation of respiration (apnoea, ataxic or cluster breathing)
- Brain swelling with depressed level of consciousness (Glasgow Coma Score <9)
- To provide control of $PaCO_2$ in patients with raised intracranial pressure
- Bulbar failure (in order to protect the airway from pulmonary aspiration)
- Encephalopathy/coma
- Cardiovascular instability (e.g. hypotension)

Table 19.13 Modes of ventilatory support.

Controlled mechanical ventilation (CMV)	Preset tidal volume at a preset respiratory rate, independent of the patient's respiratory effort Patient is completely dependent on the ventilator Used for patients who are unable to breathe or who have received neuromuscular blocking agents
Intermittent mandatory ventilation (IMV)	A mandatory minute volume is preset and delivered by the ventilator, but the patient is allowed to breathe spontaneously from a gas source between ventilator breaths
Synchronized intermittent mandatory ventilation (SIMV)	As for IMV but with coordination of the positive pressure ventilation by the ventilator so that it coincides with a spontaneous breath
Inspiratory pressure support	The patient's spontaneous breath is augmented with supplementary gas flow
Inspiratory volume support	Ventilator automatically monitors the lung properties and modifies the inspiratory pressure support in order to deliver a predetermined tidal volume
Positive end expiratory pressure (PEEP)	An adjunct to intermittent positive pressure ventilation (IPPV) and maintains a positive pressure during expiration. Helps minimize alveolar collapse and improves lung compliance
Continuous positive airway pressure (CPAP)	The application of positive airway pressure throughout all phases of spontaneous ventilation. Helps prevent airway and alveolar collapse

Weaning

Weaning of patients from mechanical ventilation may start as soon as respiratory muscle function returns; the patient needs to be able to maintain adequate oxygenation, a normal respiratory rate and appropriate spontaneous tidal volumes with minimal mechanical support. In addition, the patient needs to maintain a patent airway, to initiate cough and gag reflexes and to clear secretions independently. Sophisticated ventilatory modes discussed above aid weaning, but many units prefer to wean by allowing patients to breathe spontaneously off the ventilator for increasing periods solely with continuous positive airway pressure (CPAP).

General principles of neurological intensive care

The aim of neurological intensive care is the keen monitoring and early detection and management of impending neurological or systemic deterioration; as well as the minimization of such risk that will potentially lead to deterioration or poor outcome. There are general principles of intensive care management including meticulous nursing and medical care, monitoring of a range of physiological variables and early and aggressive physiotherapy (including frequent alterations of limb positioning, passive limb movements and appropriate splinting) which helps to maintain joint mobility and prevents limb contractures and pain while awaiting neurological improvement. Other aspects of general ICU care include the management of agitation and pain, maintenance of an adequate airway and ventilation, cardiovascular stability, nutrition and prophylaxis against thromboembolism.

Many patients with impaired consciousness or severe neuromuscular weakness are not able to communicate adequately. It is essential that satisfactory means of communication are established as soon as possible. Furthermore, when communication is difficult, the family often represents the patient's interests and they must therefore have comprehensive access to medical and nursing staff throughout so that they understand the immediate clinical situation, management and outlook.

Intracranial pressure

Intracranial pressure (ICP) is the pressure exerted by the CSF in the frontal horns of the lateral ventricles of the brain. It is normally 7–17 mmHg (1–2 kPa) when supine. Because the skull, in an adult, is a rigid box and its contents are incompressible, the

ICP depends on the volume of intracranial contents, normally approximately 100 mL blood (5–7%), 50–120 mL CSF (5–12%) and 1.4 L brain tissue (80–85%). The Monro–Kellie doctrine states that, because the total intracranial volume remains constant, any increase in the volume of any one of these components is associated with a reduction in another. The initial response to an additional volume (e.g. intracranial haematoma or swollen brain tissue) is movement of CSF into the spinal subarachnoid space, reduction of CSF volume by increased absorption by the arachnoid villi and removal of blood from the cerebrovascular bed. However, with worsening mass effect, when compensatory mechanisms are pushed to exhaustion, a relatively small increase in volume will precipitate a large rise in ICP. Recent studies show that ICP elevation itself (in the presence of well-controlled cerebral perfusion pressure [CPP] > 60) was independently associated with neurological deterioration; so even if CPP is maintained, an elevated ICP state can still aggravate neurological injury. As the ICP rises, CPP (i.e. mean arterial blood pressure [ABP] minus mean ICP) decreases, as does cerebral blood flow, particularly when cerebral autoregulation is impaired. This may lead to obstruction of venous blood vessels, brain swelling, regional ischaemia, structural distortion and the development of brainstem compression.

Intracranial pressure waveform

ICP normally has two sinusoidal waveforms that correlate with respiration and cardiac pulsation. Lundberg described three pathological waveforms associated with raised ICP, these are not typically seen on standard ICP monitors in the ICU with the typical beat-to-beat representation of the ICP waveform:

1 *A waves* (plateau waves) consist of sudden onset sustained (5–20 minutes) high amplitude (50–100 mmHg) increases in ICP which rise from and fall to normal values. These waves occur in pathological stages of raised ICP and indicate severely impaired brain compliance. They are often associated with regional or global ischaemia.

2 *B waves* are rhythmic oscillations lasting 1–2 minutes of moderate amplitude (12–50 mmHg) increases in ICP. They may occur in mechanically ventilated patients or in association with Cheyne–Stokes respiration but they are an indication of failing compensation and incipient sustained rises in ICP.

3 *C waves* are of longer duration (4–8/minute) and smaller amplitude (<20 mmHg). These are widely believed to be non-pathological and represent physiological variability (Figures 19.4 and 19.5).

Raised intracranial pressure

Raised ICP in the conscious patient is characterized by headache, which may be exacerbated by coughing, sneezing or straining. It is often worse on wakening and associated with nausea and vomiting. The diurnal variation in headache is caused by raised ICP when recumbent and associated raised $PaCO_2$ and reduced CSF absorption during sleep. A reduced level of consciousness is an almost universal finding in patients who have significant acute herniation syndromes; with or without ICP elevation. In severely raised ICP this is accompanied by Cushing's triad (bradycardia, hypertension and respiratory irregularity). It is important to note that raised ICP is not always observed in a herniation event despite the presence of a dilated pupil. Other focal signs of raised ICP can point to tentorial or tonsillar herniation, and eventually brainstem compression or distortion.

Raised ICP may be unvarying, particularly following head injury when the level reflects the severity of the insult (severe >20 mmHg). However, the presence of fluctuations and, in particular, A and B waves, indicates rapid deterioration because of vasogenic change and suggests that intracranial hypertension leading to herniation will develop unless urgent intervention is undertaken (Figure 19.6).

Measurement of intracranial pressure

A variety of different techniques are available for the measurement of ICP. Intraventricular fluid filled catheter transducer systems require an external pressure transducer connected to a catheter placed in the lateral ventricle to allow direct pressure management. It is the most accurate technique for ICP measurement as the system can be recalibrated as required and allows drainage of CSF. It is not limited by intercompartment pressure gradients provided all the ventricles are in communication. However, these catheters are associated with a risk of infection, haematoma formation and seizures and are difficult to place in small ventricles which are common if raised ICP is caused by brain swelling.

More commonly, a catheter tip transducer system is used to record from the ventricle, subdural or subarachnoid space or parenchyma. This is usually undertaken with a catheter tip transducer inserted via an airtight support bolt (e.g. Codman© or Camino©). These systems are slightly less reliable, require pre-insertion calibration and may fail after several days, but the ease of placement has led to their widespread use in patients with cerebral trauma.

Indications for intracranial pressure monitoring

ICP monitoring is undertaken as a guide to treatment or, less commonly, as a diagnostic investigation. Clinical and radiological evidence is not always a reliable guide to raised ICP and monitoring is necessary if there is an unstable haemodynamic state or a mass lesion indicating the possibility of incipient herniation.

Evidence supports the routine use of ICP monitoring in patients with severe head injury (GCS 3–8) and an abnormal CT scan (see below), significant focal motor signs or hypotension. ICP monitoring may be helpful following subarachnoid haemorrhage, intracerebral haemorrhage, venous sinus thrombosis or following hypoxic brain injury, encephalitis or hepatic encephalopathy. It may also be of diagnostic value in patients with normal pressure hydrocephalus, idiopathic intracranial hypertension or decompensated hydrocephalus.

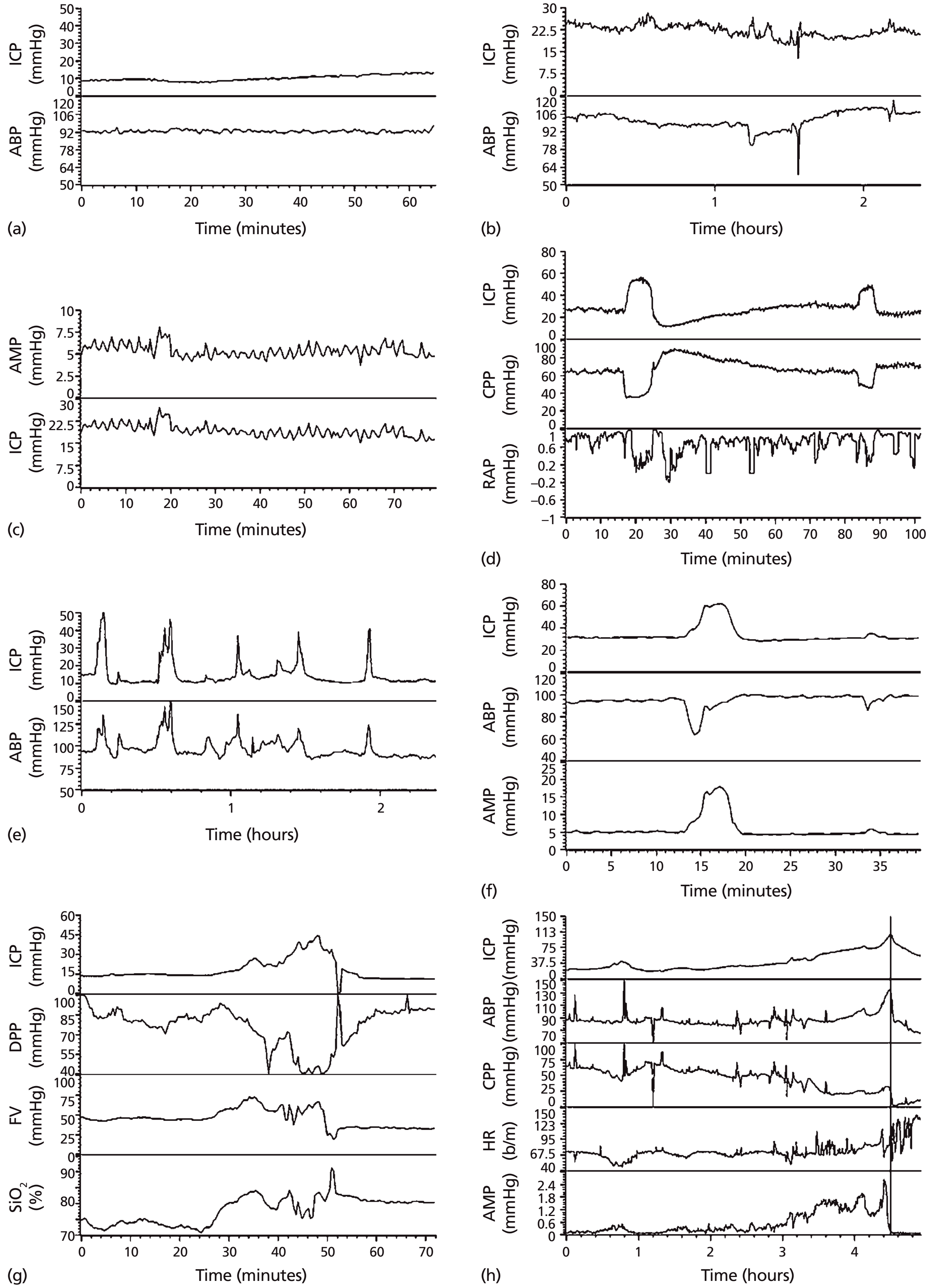


Figure 19.4 Intracranial pressure monitoring. (a) Low and stable intracranial pressure (ICP). Mean arterial blood pressure (ABP) is plotted along the lower panel. (b) Stable and elevated ICP. This can be seen most of the time in head injury patients. (c) 'B' waves of ICP. They are seen both in mean ICP and spectrally resolved pulse amplitude of ICP (AMP, upper panel). They are also usually seen in plots of time averaged ABP, but not always. (d) Plateau waves of ICP. Cerebrospinal compensatory reserve is usually low when these waves are recorded (RAP correlation coefficient [R] between AMP amplitude [A] and mean pressure [P]) close to +1; index of compensatory reserve. At the height of the waves, during maximal vasodilatation, integration between pulse amplitude and mean ICP fails as is indicated by fall in RAP. After the plateau wave, ICP usually falls below baseline level and cerebrospinal compensatory reserve improves. (e) High, spiky waves of ICP caused by sudden increases in ABP. (f) Increase in ICP caused by temporary decrease in ABP. (g) Increase in ICP of 'hyperaemic nature'. Both blood flow velocity and jugular venous oxygen saturation (SjO_2) increased in parallel with ICP. (h) Refractory intracranial hypertension. ICP increased within a few hours to above 100 mmHg. The vertical line denotes the moment when the ischaemic wave probably reached the vasomotor centres in the brainstem: heart rate increased and ABP (cerebral perfusion pressure) decreased abruptly. Note that the pulse amplitude of ICP (AMP) disappeared around 10 minutes before this terminal event. (After Czosnyka MJ, Pickard JD. *J Neurol Neurosurg Psychiatry* 2004; **75**: 813–821 with permission from the publishers.)

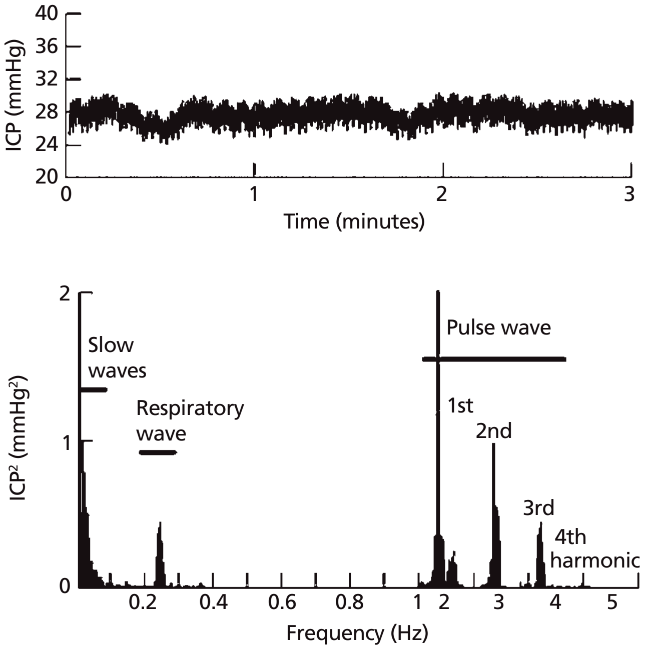


Figure 19.5 Example of intracranial presure (ICP) recording showing pulse, respiratory, and 'slow waves' overlapped in time domain (upper panel). (After Czosnyka MJ, Pickard JD. *J Neurol Neurosurg Psychiatry* 2004; **75**: 813–821 with permission from the publishers.)

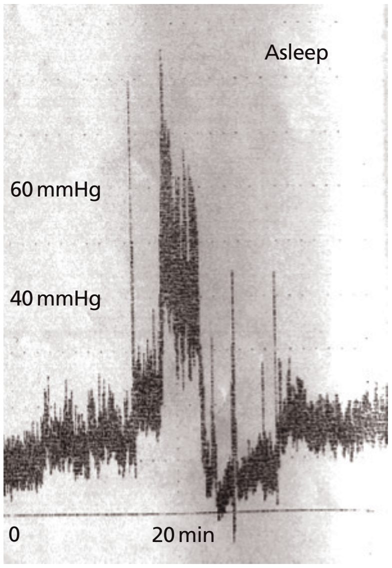


Figure 19.6 Intracranial pressure (ICP) trace for a patient with a plateau of high ICP.

Management

Urgent treatment of raised ICP may be necessary to avoid development and progression of herniation and subsequent brain ischaemia, infarction and death. If ICP exceeds 20 mmHg treatment is mandatory. The first line of management of raised ICP is to ensure a secure airway and maintain systemic arterial blood pressure. Treatment of the underlying cause, where possible, should be undertaken urgently and aggressive control of metabolic derangements, seizures and pyrexia is essential. CPP must be maintained by ensuring optimal arterial blood pressure with avoidance of hypotension; this requires careful intravenous fluid management and the use of inotropic agents. Neuromuscular blockade, sedation and analgesia are needed to help avoid surges in ICP from suctioning, coughing or other interventions such as physiotherapy.

Head positioning

The head should be elevated to 30° to facilitate venous drainage. Any constriction around the neck (e.g. tracheal tube ties) must be avoided as this may obstruct cerebral venous drainage.

Controlled hyperventilation

Hyperventilation lowers $PaCO_2$ and induces cerebral vasoconstriction reducing cerebral blood volume. This is a rapid, effective way of reducing elevated ICP but is limited by a contingent reduction in cerebral blood flow (CBF) to any area of critical perfusion. Patients are therefore ventilated to a $PaCO_2$ of 4 kPa. Beneficial effects of hyperventilation are often transient and it should only be used for 10–20 hours and then weaned slowly. After this, tolerance can develop; rebound vasodilatation may lead to rebound increase in ICP. Hyperventilation should be used only during the time of acute neurological deterioration; chronic hyperventiliation and 'prophylactic hyperventiliation' is not recommended because it leads to worse injury and poorer outcome.

Osmotic agents

Mannitol is a hyperosmolar diuretic that lowers ICP and increases CBF by reducing interstitial water content. This effect is achieved by establishing an osmotic gradient between blood and brain parenchyma. Several additional effects have been reported, including acting as a plasma expander to reduce blood viscosity, a decrease in CSF production and an increased cardiac preload. However, with prolonged therapy, mannitol may diffuse into damaged brain cells and exacerbate tissue oedema. It is also associated with a hyperosmotic state and leads to a profound diuresis with consequent fluid management difficulties. Furosemide and thiazide diuretics may also be used. It is important to emphasize that diuresis leading to intravascular volume compromise is not the target of this therapy. The goal is to increase osmolarity in the vascular compartment and maintain the intravascular volume; therefore, intake and output needs to be monitored carefully and fluid, in the form of more concentrated isotonic solutions, needs to be replaced. It is also important to emphasize that, as CPP = MAP – ICP, if the mean arterial pressure (MAP) is decreased because of overzealous diuresis then CPP will be similarly impaired; furthermore, systemic hypotension leads to reflex intracranial vasodilatation which in turn increases ICP.

CSF drainage via an intraventricular catheter

This may be undertaken intermittently in response to elevations in ICP. However, ventriculostomy is associated with a risk of perioperative haemorrhage and secondary infection thereafter.

Other interventions

Barbiturate-induced coma reduces cerebral metabolic activity and causes cerebral vasoconstriction which leads to a reduction in CBF, cerebral blood volume and consequently ICP but may be accompanied by a high incidence of side effects, particularly hypotension.

Hypothermia

Hypothermia can lower ICP by decreasing cerebral metabolism. Moderate hypothermia (35°C) decreases raised ICP but lower body temperatures cause cardiac arrhythmias and coagulation disturbances. Raised body temperature is deleterious as it increases ICP and must therefore be treated aggressively. Hypothermia is now widely used in combination with other therapies for lowering raised ICP.

Fever control

Temperature elevation contributes to more harm, by vasodilatation, an increase in intracranial mass and thus more neuronal injury. Adequate control of pyrexia is essential.

Decompressive surgery

This has been increasingly used following extensive traumatic brain injury and middle cerebral artery occlusion, intracranial haemorrhage, subarachnoid haemorrhage or severe encephalitis. Some reports suggest good recovery; there is a high incidence of severe residual morbidity.

Cerebral herniation

Cerebral herniation is an important mechanism of coma and permanent neurological impairment. It occurs when raised ICP leads to torsion and compression of the brainstem against the tentorium, falx and bony structures.

Herniation of the temporal lobe through the tentorium (uncal herniation)

This is caused by asymmetrical mass effect causing the temporal lobe, uncus and hippocampus to shift towards the midline leading to compression of the midbrain against the tentorial edge (Figure 19.7). The initial manifestation of incipient uncal herniation is involvement of the IIIrd nerve ipsilateral to the mass lesion, initially causing a sluggish reaction to light which is followed by fixed pupillary dilatation. Alteration of consciousness occurs because of involvement of the anterior reticular activating system (RAS). Following this there may be compression of the ipsilateral posterior cerebral artery against the tentorial edge which may lead to occlusion and haemorrhagic infarction of the occipital lobe. The herniated uncus causes the midbrain to be shifted and compressed against the rigid dura on the contralateral side causing damage to the cerebral peduncles (particularly affecting fibres that project to the leg) leading to a hemiparesis ipsilateral to the lesion and IIIrd nerve palsy. The rigid tentorium carves out a notch on the lateral aspect of the midbrain (Kernohan's notch phenomenon). Tearing of the paramedian perforating vessels is caused by torsion, anteroposterior elongation and downward displacement of the midbrain and leads to consequent brainstem infarction and haemorrhage. The dilated pupil may become a little smaller as the sympathetic pathway in the brainstem is damaged, while with further brainstem compression, the other pupil becomes midsized and unresponsive. Established oculomotor paresis appears, first in the eye originally involved and shortly afterwards in the other eye.

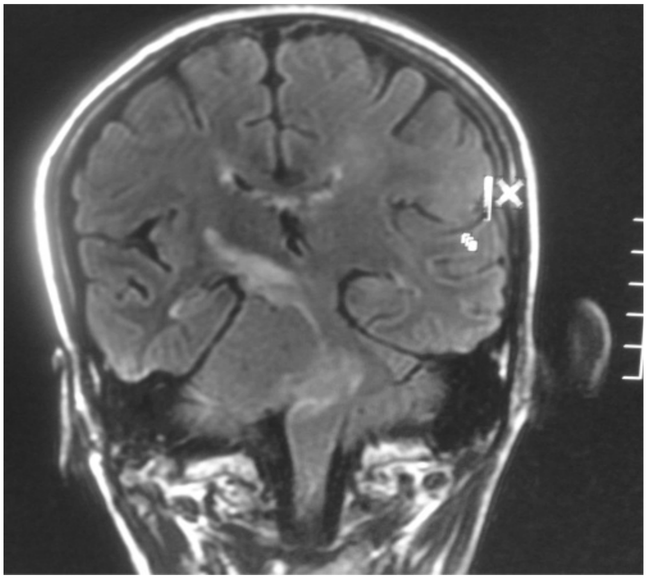


Figure 19.7 Uncal herniation from a large cerebellar-pontine angle meningioma.

Survivors of tentorial herniation may be left in a locked-in or vegetative state or may demonstrate other signs of residual brainstem damage including oculomotor nerve dysfunction, INO, vertical gaze paresis, homonymous hemianopia or blindness, pyramidal limb weakness, parkinsonism or other extrapyramidal syndromes.

Central herniation of the brainstem

This occurs as a result of diffuse symmetrical raised ICP often because of cerebral oedema or obstructive hydrocephalus. Downward displacement of the hemispheres leads to compression of the diencephalon and midbrain and descent through the tentorial notch. Characteristic clinical patterns of brainstem descent have been described by Plum and Posner, but these are now rarely observed in clinical practice because of earlier therapeutic intervention. Initially, compression of the midbrain leads to impairment of concentration and alertness leading to progressive somnolence and reduced levels of consciousness. The pupils remain reactive but constricted, because of involvement of autonomic pathways, and roving eye movements are gradually lost with progressive compression. With increased supratentorial pressure there is a further downward shift leading to compression and torsion of the pons with rupture of the paramedian perforating arteries supplying the tegmentum of the midbrain and pons. With progressive descent of the brainstem the patient becomes deeply unconscious with abnormal patterns of respiration and temperature control. The pupils are unequal, unreactive, mid-sized and irregular. VOR may elicit restricted vertical gaze, but a progressive total ophthalmoplegia develops. Eventually there may be decerebrate posturing to painful stimuli prior to the development of hypotension, apnoea and cardiac arrhythmia.

Subfalcine herniation

This occurs when the cingulate gyrus is displaced across the midline and under the falx. It is usually caused by a structural lesion in the frontal lobe but may follow a traumatic injury. This may lead to compression of the ipsilateral anterior cerebral artery with secondary frontal infarction and oedema.

Upward transtentorial herniation

Upward transtentorial hernation of the brainstem may rarely occur as a result of lesions that compress the upper brainstem including tumour or haemorrhage in the pons, cerebellum or region of the 4th ventricle, particularly if any resulting hydrocephalus is drained. The tectum of the midbrain and the anterior cerebellar lobules are forced upwards through the tentorium leading to signs of brainstem dysfunction – small, asymmetrical and fixed pupils, vertical ophthalmoplegia and abnormal respiratory patterns leading to decerebrate posturing and coma.

Tonsillar herniation

Tonsillar herniation occurs if there is downward displacement of inferior medial cerebellar tonsils into the foramen magnum. This may be caused by an Arnold–Chiari malformation or a posterior fossa mass lesion. Some patients may be awake in the early stages because there is no compression of the RAS. There may be progressive medullary compression and ischemia characterized by a sudden respiratory arrest with quadriplegia or the development of a stiff neck, vomiting, skew deviation of the eyes, respiratory irregularity, coma and death.

Traumatic brain injury

Damage to the brain following trauma includes the immediate, or primary, injury caused at the moment of impact, and the secondary injury that develops in the first few hours or days after the impact which may be a result of extracranial or intracranial causes.

1 *Primary brain injury*
  Disruption of brain vessels
  Haemorrhagic contusion
  Diffuse axonal injury
2 *Secondary brain injury*
Extracranial causes
  Systemic hypotension (systolic BP < 90 mmHg)
  Hypoxaemia ($PaO_2 < 60$ mmHg)
  Hypercarbia (high blood CO_2)
  Disturbances of blood coagulation
Intracranial causes
  Haematoma (extradural, subdural or intracerebral)
  Brain swelling
  Infection

At present no neuroprotective agent has been shown to reduce primary brain injury; however, secondary insults, which further exacerbate neuronal injury and lead to a poorer outcome, are often preventable with prompt intervention. Over one-third of all severe traumatic brain injury patients develop either or both hypoxia or hypotension during the acute post-injury period. These secondary insults are correlated with a large increase in morbidity and mortality.

Skull fractures

Skull fractures occur three times more commonly in the vault than the base of the skull and are associated with a high incidence of intracranial haematomas. If the fracture is closed and is not depressed, specific treatment is rarely required and healing occurs spontaneously; however, open and depressed fractures require surgical intervention. Clinical indicators of a base of skull fracture include periorbital bruising (panda or racoon eyes), retro-auricular bruising (Battle's sign) and an associated CSF leak from the nose (rhinorrhoea) or the ears (otorrhoea). Eighty per cent of leaks close spontaneously but bacterial meningitis may complicate a CSF leak in some cases. No studies have shown convincing evidence regarding the efficacy of routine antibiotic prophylaxis for skull fractures.

Focal lesions

Approximately one-quarter of all patients with traumatic brain injury have an operable intracranial haematoma.

Extradural haematoma

An extradural haematoma (EDH; Figure 19.8) is an accumulation of blood in the extradural space between the inner side of the skull and the dura mater. Most (90%) are associated with skull fracture and are caused by injury of the middle meningeal artery, therefore affecting the parietal and tempero-parietal areas. Rarely, a fracture may be associated with tearing of large veins at the vertex of the skull or of the venous sinuses. Associated brain contusion is less common than with subdural haematoma (SDH). The outcome depends on the level of consciousness at the time of surgery, with mortality approaching 20% if the patient is unconscious prior to surgery. Patients with a skull fracture may be neurologically intact on admission but, more often, primary brain damage has caused some disturbance of consciousness and the developing haematoma results in rapid neurological deterioration.

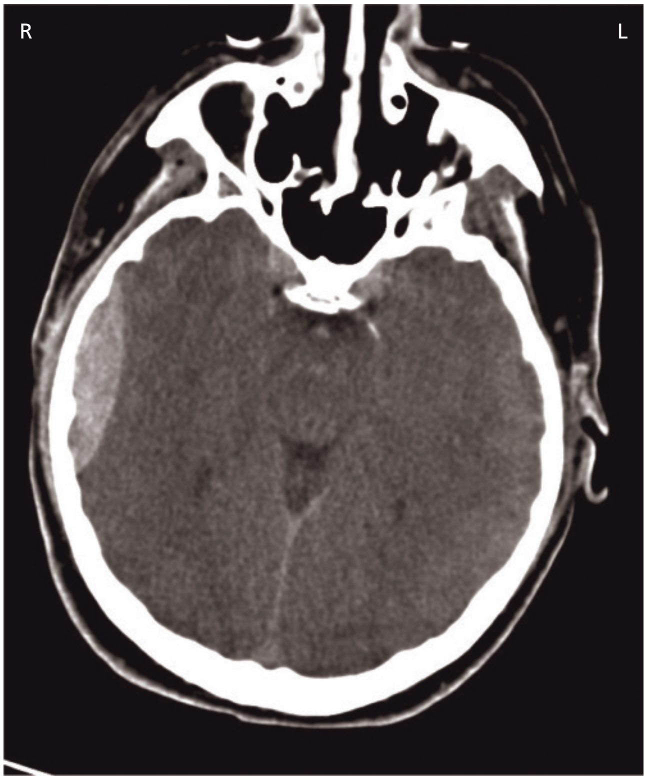


Figure 19.8 CT scan showing acute extradural haematoma.

Subdural haematoma

An SDH is an accumulation of blood between the inner side of the dura and the arachnoid layer (Figure 19.9). It is either due to tearing of cortical veins when the haemotoma is usually frontal, or small arteries, when it is more often tempero-parietal. Most patients with acute SDHs have some kind of accompanying brain injury and their prognosis is worse than those with EDHs. The patient is usually unconscious or there is impaired alertness, cognition and focal signs and continued deterioration is usual. A poor outcome is more likely if the trauma is severe with underlying brain contusion, the SDHs are bilateral, accumulated rapidly, or if there was >4 hours delay in surgical management. CT imaging allows assessment of skull fracture, contusion and haemorrhage but SDH may be isodense 1–3 weeks after onset or in the presence of anaemia; therefore, in the subacute or chronic state MRI is preferable.

Chronic SDH can develop many weeks or months after head injury. The injury may be minor and the patient may not remember a particular event. Predisposing factors include increasing age, alcoholism, coagulopathy, epilepsy and the presence of ventricular drains (Figure 19.9). The most common symptom is headache, which worsens progressively and is associated with a fluctuating level of consciousness, focal signs and raised ICP. The treatment of choice is evacuation of the subdural collection and irrigation with isotonic saline at body temperature. Small SDHs can be treated conservatively.

Traumatic subarachnoid haemorrhage

Traumatic subarachnoid haemorrhage (SAH) is seen in 30–40% of patients following severe traumatic brain injury (TBI) but must be quantified on early CT scan because later scans underestimate its incidence and severity. Its presence indicates a worse outcome following TBI (Figure 19.10).

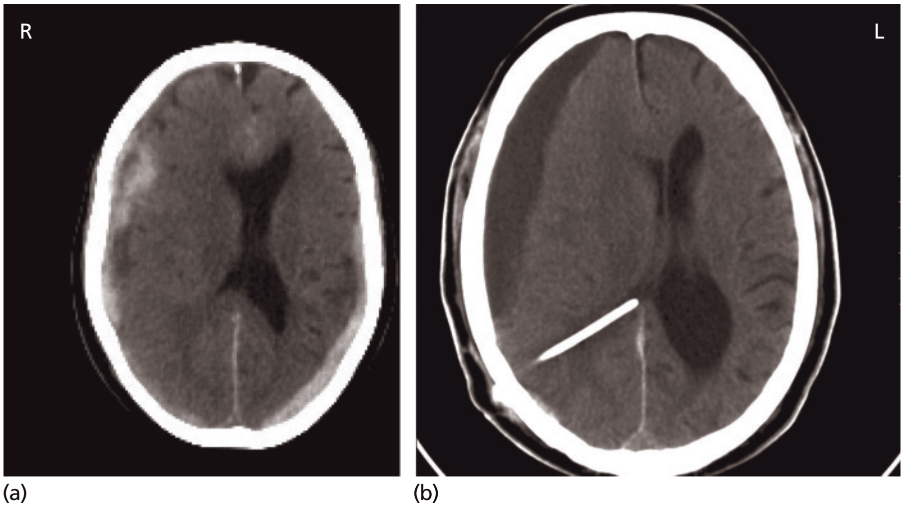


Figure 19.9 CT scan showing: (a) extensive fresh bilateral acute subdural haematoma with midline shift; and (b) large chronic subdural haematoma following insertion of intraventricular shunt.

Haemorrhagic contusions and lacerations

Haemorrhagic contusions and lacerations (Figure 19.11) are superficial areas of haemorrhage usually affecting the frontal and temporal lobes. They are usually caused by venous injury sustained as the brain hits the bony protruberances of the skull at the site of impact and then the opposite side during deceleration (contrecoup injury). The term contusion is used when the pia mater has not been breached, and laceration when the pia mater is torn. Local areas of contusion with no or minimal blood flow are common after severe TBI and the centre of the contusion is often irreversibly damaged. However, areas around the contusion (penumbra) are associated with localized cerebral oedema and have survival potential if the oxygen supply to this region is maintained. Focal contusions can be associated with cerebral oedema and raised ICP leading to delayed neurological deterioration and may need surgical evacuation.

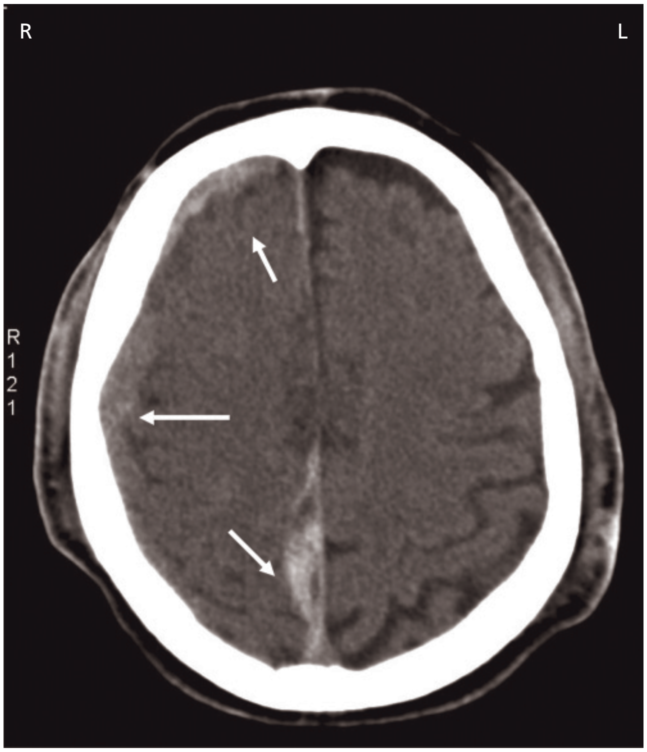


Figure 19.10 CT scan showing traumatic subarachnoid haemorrhage. Arrows show right anterior and lateral subdural blood collections and parafalcine subarachnoid collection.

Intracerebral haematoma

Intracerebral haematoma (ICH) usually occurs as a result of direct trauma to intracranial vessels and affects the frontal and temporal lobes or basal ganglia. It is a cause of delayed neurological deterioration in <20% of patients with severe TBI particularly if there is a coagulopathy.

Diffuse axonal injury

Diffuse axonal injury (DAI) occurs in 50–60% of patients with severe head injury and is the most common cause of coma, the vegetative state and subsequent disability (Figure 19.12). Neuropathologically severe DAI has three components:

1 A focal lesion in the corpus callosum, often associated with traumatic intraventricular haemorrhage;

2 Focal lesions in the brainstem; and

3 Microscopically widespread damage to axons, often associated with scattered small haemorrhages and mainly located along or near the midline.

DAI is attributed to shearing of nerve fibres at the junction between the grey and white matter because they decelerate at different velocities within the skull. Recent data suggests that

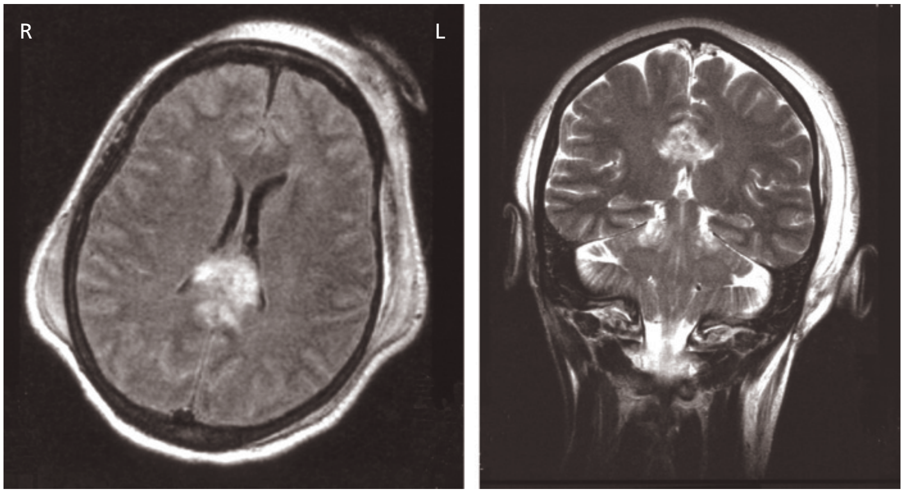


Figure 19.11 Diffuse axonal injury showing extensive haemorrhagic change in the region of the splenium (MRI T1-weighted axial and coronal).

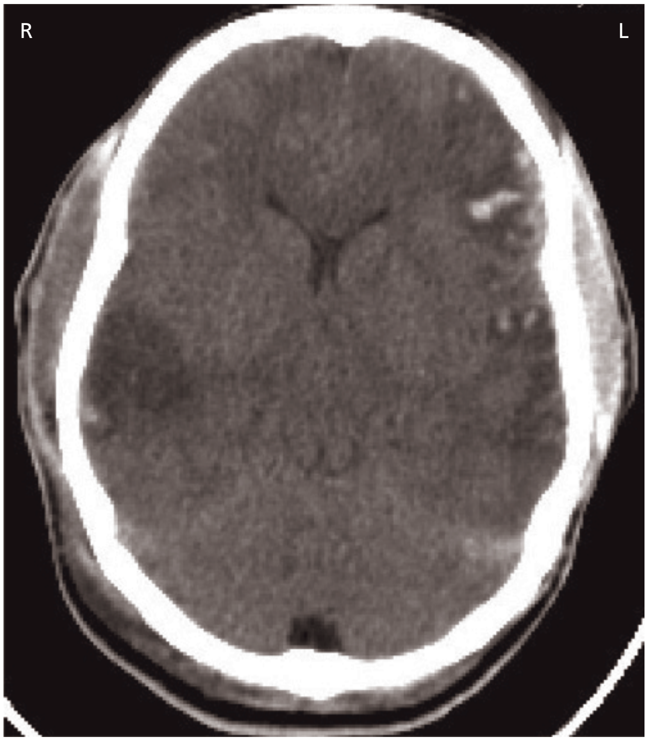


Figure 19.12 CT scan of patient with traumatic brain injury (TBI) showing extensive left temporal contusion and laceration with contre coup injury in right parietal region.

DAI is a dynamic process at a cellular level that begins soon after trauma and may not be complete for over 24 hours. Outcome is usually poor, with the mortality for severe DAI approaching 50%. Patients with severe DAI are often in deep coma despite imaging showing only scattered punctate lesions and a normal ICP.

Cerebral ischaemia

Cerebral ischaemia, whether brought about by hypoxia, hypotension or intracranial hypertension, dominates severe TBI and is the single most important factor in determining outcome, with ischaemic lesions being found in 90% of patients at postmortem. Cerebral ischaemia will arise whenever the delivery of oxygen and substrates to the brain falls below its metabolic needs. Areas of focal ischaemia occur in <50% of patients with SDH or DAI but are rare in patients with EDH or normal imaging. Blood flow in and around areas of brain tissue damaged by trauma may be abnormal because vasomotor paralysis and loss of autoregulation leads to loss of blood pressure control and reactivity to CO_2. CBF therefore becomes pressure-dependent, rendering this area of brain more susceptible to ischaemia at lower blood pressures and more likely to sustain injury at higher pressures.

Table 19.14 Indications for decompressive surgery.

Intracranial mass lesions with midline shift or basal cistern compression on CT scan
A surgically significant EDH or acute SDH needs evacuation within 2–4 hours of injury to achieve optimal chance of recovery
For small haemorrhagic contusions or other small intracerebral lesions a conservative approach is generally adopted but operation should be considered urgent for a large ICH (>20–30 mL) based on position, clinical condition and ICP
Skull fractures that are depressed > the thickness of the skull or compound fractures with torn dura require surgery

CT, computed tomography; EDH, extradural haematoma; ICH, intracerebral haematoma; ICP, intracranial pressure; SDH, subdural haematoma.

Intensive care management of TBI

The aim of intensive care management of the head-injured patient is to prevent and treat secondary physiological insults.

Monitoring

Monitoring of ECG, direct arterial blood pressure, central venous pressure and pulse oximetry is mandatory in all patients. An oesophageal Doppler monitor or pulmonary artery catheter may assist in directing therapy in those patients with cardiovascular instability or in whom cardiovascular targets are difficult to achieve. Regular arterial blood gas analysis, measurement of blood glucose and sodium and core temperature monitoring are also required to optimize treatment strategies. Cerebral monitoring allows measurement of CPP, estimation of CBF and assessment of the adequacy of oxygen delivery to the brain. This allows therapy to be targeted to specific changes in brain function and to ensure a balance between cerebral metabolic supply and demand. Monitoring may include measurement of ICP (as above), transcranial Doppler ultrasonography (TCD) of blood flow velocity in the middle cerebral artery and jugular venous bulb oximetry to assess the balance between cerebral oxygen supply and demand after head injury.

ICP after TBI

Conventional approaches to the management of head-injured patients have concentrated on a reduction in ICP to prevent secondary ischaemic insults. Uncontrolled intracranial hypertension remains an important cause of morbidity and mortality after severe TBI. ICP > 20 mmHg and CPP < 60 mmHg are powerful predictors of outcome together with age, admission GCS and pupillary signs. Aggressive management, based on ICP monitoring, significantly reduces the overall mortality rate without causing a disproportionate number or severely disabled or vegetative patients.

The indications for decompressive surgery are summarized in Table 19.14 and EBIC Guidelines for the management of Severe Head Injury in Adults are shown in Table 19.15.

Table 19.15 Guidelines for the management of severe head injury in adults (after European Brain Injury Consortium and Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons; Joint Section on Neurotrauma and Critical Care).

Monitoring and general care

Minimal monitoring requirements include ECG, SaO$_2$, invasive ABP, temperature and end-tidal CO$_2$
Maintain SaO$_2$ > 95%, MABP > 90 mmHg
Central venous pressure monitoring to ensure normovolaemia
If ICP monitored – continuous monitoring of ABP and calculation of CPP

Ventilatory parameters

Adjust ventilation to maintain PaO$_2$ > 13 kPa (100 mmHg) and PaCO$_2$ 4.0–4.5 kPa (30–35 mmHg)

Management of ICP and CPP

Treat ICP elevations above 20–25 mmHg
Maintain CPP > 60 mmHg
There is no consensus whether patients should be nursed flat or with the head up to a maximum of 30° elevation

Accepted methods of management of ICP and CPP

Sedation
Analgesia
Mild to moderate hyperventilation (PaCO$_2$ 4.0–4.5 kPa, 30–35 mmHg)
Volume expansion and inotropes or vasopressors when ABP insufficient to maintain CPP in a normovolaemic patient
Osmotic therapy (preferably mannitol, repeated in bolus infusions, maintaining serum osmolarity ≥315)
If osmotherapy has insufficient effect, frusemide can be given additionally
CSF drainage
If these methods fail, more intensive hyperventilation (PaCO$_2$ < 4.0 kPa or 30 mmHg), preferably with monitoring by jugular oxymetry of cerebral oxygenation to detect ischaemia
Alternatively, the use of barbiturates, inducing increased sedation, may be considered
There is no established indication for steroids in the management of acute head injury

Timing and indications for operative therapy

A surgically significant EDH or ASDH should be evacuated immediately upon detection
For small haemorrhagic contusions or other small intracerebral lesion, a conservative approach is generally adopted, but operation should be considered urgent for large intracerebral lesions with high or mixed density on CT scan
Depressed skull fracture: operation is definitely indicated only if it is a compound (open) fracture (not over sagittal sinus) or if the fracture is so extensive that is causes mass effect
Closed depressed skull fractures are usually treated conservatively, but operation may be appropriate in selected cases to reduce mass effect or correct disfigurement
Decompressive craniotomy may be considered in certain situations

ABP, arterial blood pressure; ASDH, acute subdural haematoma; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; CT, computed tomography; EDH, extradural haematoma; ICP, Intracranial pressure; MABP, mean arterial blood pressure; SaO$_2$, arterial oxygen saturation.

Hydrocephalus and shunts

Hydrocephalus may be defined as excessive CSF; the causes are multitudinous but in principle it may be caused by excess production, altered flow through the ventricular system and/or impaired reabsorption into the venous system circulation via the arachnoid granulations. Such is the importance of CSF that Harvey Cushing, the founder of neurosurgery, called it the 'fourth circulation'.

Clinically, hydrocephalus may be divided up into communicating and non-communicating or obstructive and non-obstructive hydrocephalus. Communicating (non-obstructive) hydrocephalus denotes an enlarged ventricular system but normal communication and flow between the ventricles and the extracerebral CSF. The aetiology is impaired absorption. Non-communicating (obstructive) hydrocephalus results from obstruction to the normal CSF pathways. Sometimes both these categories of hydrocephalus are quite distinct, e.g. communicating hydrocephalus secondary to subarachnoid haemorrhage and non-communicating hydrocephalus secondary to, for example, a colloid cyst of the third ventricle. However, both communicating and non-communicating aetiologies may coexist, e.g. an interventricular or skull base tumour causing some obstruction but also producing a highly proteinaceous CSF or chronic meningitis leading to impaired reabsorption of CSF. It is also important to differentiate between acute hydrocephalus (which has more rapid and devastating consequences including herniation and death) and chronic hydrocephalus. In addition, there are a number of specific and somewhat confusing terms. Arrested hydrocephalus applies to those adult patients who have some developmental hydrocephalus and abnormality of the brain development resulting in large ventricles and often large heads but who are well. Occasionally, these patients decompensate later in life and can present with headaches and/or ataxia or more acutely following what would otherwise be a minor head injury. Hydrocephalus *ex vacuo* describes ventriculomegaly secondary to cerebral volume loss for any reason. Normal pressure hydrocephalus (NPH) describes a mild degree of hydrocephalus where the CSF pressure is intermittently raised. Clearly, this condition of NPH and hydrocephalus *ex vacuo* would need to be distinguished in the elderly population where the rare triad of cognitive failure, urinary incontinence and gate apraxia associated with NPH may be incomplete.

The presenting features of hydrocephalus depend on its aetiology and rate of development and the presence of raised ICP. For example, a sudden collapse into coma and even sudden death can occur in rare instances of colloid cysts obstructing the third ventricle outflow, whereas the gradual development of non-communicating hydrocephalus will result in headache and papilloedema progressing to a gait disturbance before more obvious symptoms and signs of raised ICP develop.

Investigations

CT or magnetic resonance imaging (MRI) will define ventricular size and therefore show ventriculomegaly; they will also give an indirect indication of raised ICP (e.g. periventricular lucency, ventricular to sulcal effacement and differential size of the different parts of the ventricular system). It is important to reflect on both the ventricular volume and the presumptive pressure before deciding on a management plan. The investigatory algorithm for suspected NPH patients is controversial. Walking tests following lumbar puncture, lumbar infusion and concomitant ICP measurements as well as isotope cisternography have been used to determine the pressure–volume relationship.

Management

Frequently, conservative management is appropriate, particularly in those cases of arrested hydrocephalus (i.e. ventriculomegaly but no raised pressure). The mainstay of active treatment involves either a shunt or third ventriculostomy. With a shunt procedure CSF is channelled via a hollow silicon tube between the ventricular system and usually the peritoneum. Other sites can be used such as the right atrium and occasionally the pleura. Shunts have the distinct advantage of being simple and now relatively reliable. However, they do have a failure rate that accumulates over time secondary to blockage and they can also become infected despite the numerous proprietary attempts to either impregnate them with antibiotics and/or the use of non-touch techniques by surgeons and perioperative antibiotics. The shunts themselves range from the very simple to those with anti-siphon devices and programmable options where the flow may be altered to suit the response of the patient and his or her imaging. These may be particularly appropriate in those patients of relatively low raised pressure, typically NPH where over-drainage would be a serious complication.

Endoscopic third ventriculostomy is an increasing used technique in which a hole is fashioned in the thinned floor of the third ventricle such that the ventricular CSF communicates directly with the basal cisterns. This is particularly useful in cases of aqueduct stenosis or tumours in the posterior fossa and midbrain and thus this technique is far more common in paediatric than adult cases. In the acute clinical situation, such as hydrocephalus secondary to meningitis or subarachnoid haemorrhage, particularly where the protein level is very high and/or when intrathecal antibiotics are to be administered, then a temporary shunt or external ventricular drain is inserted, which may be converted to a shunt at a later date. Finally, lumboperitoneal shunts are used on occasion, particularly when there is a technical issue in cannulating the ventricular system, usually when the ventricles are small and the pressures are high and very typically in benign intracranial hypertension (BIH).

Stroke

The principles of assessment and resuscitation from acute stroke are similar regardless of the underlying cause and include the following:

- Airway management – tracheal intubation is indicated when there is:
  - impaired level of consciousness (GCS < 9)
  - progressive respiratory impairment or respiratory failure
  - impaired cough and airway clearance
  - pulmonary oedema/aspiration
  - seizure activity
  - a need for diagnostic or therapeutic procedures such as MRI or thrombolysis;
- Maintenance of adequate arterial blood pressure–cerebral perfusion pressure;
- Intravenous fluid management;
- Temperature control;
- Control of seizures;
- Institution of enteral nutrition;
- ICP management;
- Medical treatment of complications (e.g. sepsis);
- Other management related to the underlying cause (e.g. anticoagulation, thrombolysis, evacuation of haematoma, clipping and coiling of intracerebral aneurysms).

See also Chapter 4.

Middle cerebral artery occlusion

Late clinical deterioration following stroke is common and depends on the severity, localization and pathology. Acute middle cerebral artery occlusion is associated with cerebral oedema, which usually develops after 2–7 days. Oedema and infarction causes a mass effect leading to horizontal and vertical distortion and shift of the brainstem. This change in dynamics may not be

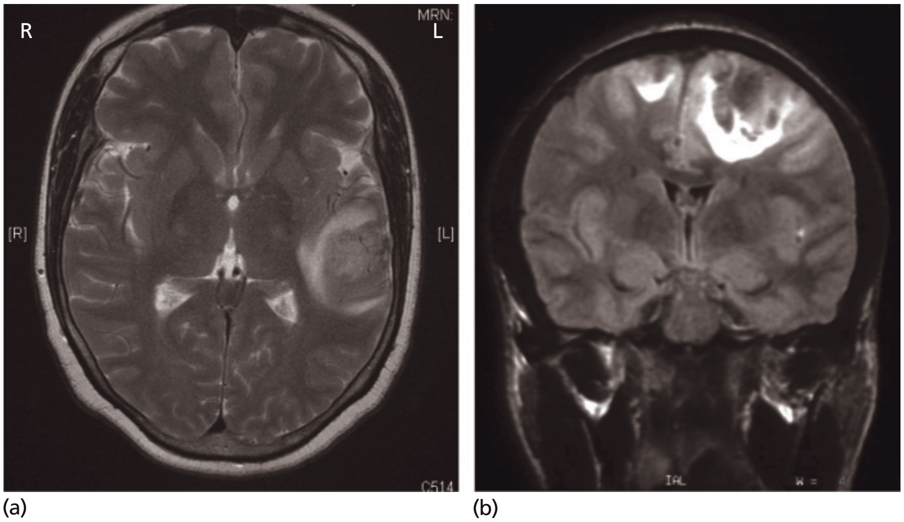


Figure 19.13 Extensive haemorrhagic cortical venous thrombosis. (a) T2 axial MRI; (b) T1 coronal MRI.

reflected by ICP monitors. Other causes of deterioration include haemorrhagic conversion of the infarct, which may produce diencephalic brain herniation, the development of seizures and systemic factors including congestive cardiac failure, pulmonary oedema, cardiac arrhythmias or pulmonary emboli.

Acute basilar occlusion

Following acute basilar occlusion, late deterioration occurs in up to one-third of patients because of extension of the thrombus causing successive occlusion of the perforating arteries or because of emboli arising from the occluded vessel.

Cerebellar infarcts

These are associated with progression of infarction leading to brainstem involvement and herniation, late brainstem compression arising from cerebral oedema around the infarct, the development of hydrocephalus from obstruction of 3rd and 4th ventricles, aqueduct or outflow and systemic complications. Occasionally, decompressive surgery is necessary.

Subarachnoid haemorrhage

Sudden death may occur following subarachnoid haemorrhage in up to 10% because of early rebleeding, intraventricular extension of the haemorrhage or complications including pulmonary aspiration, cardiac arrhythmias and neurogenic pulmonary oedema. Clinical deterioration may also develop because of delayed cerebral ischaemia from progressive vasospasm, enlargement of intracerebral haematoma or the development of hydrocephalus.

Supratentorial intracerebral haemorrhage (basal ganglia or lobar)

This is associated with enlargement of the haematoma, development of surrounding oedema, obstructive hydrocephalus or systemic complications including aspiration pneumonia, sepsis or cardiac arrhythmias.

Infratentorial intracranial haemorrhage (cerebellar or brainstem)

Following infratentorial intracranial haemorrhage (cerebellar or brainstem), clinical deterioration is commonly caused by direct brainstem compression accompanied by cerebellar herniation rather than obstructive hydrocephalus. Rebleeding is a neurosurgical emergency and the high mortality often justifies surgical evacuation.

Cerebral venous thrombosis

Late complications of cerebral venous thrombosis include extension of the thrombosis, development of haemorrhagic infarction, raised ICP secondary to cerebral oedema, seizures, the development of systemic complications including aspiration pneumonia, pulmonary emboli and sepsis, and complications of a hypercoagulable state (Figure 19.13).

Status epilepticus

Following adequate resuscitation, the treatment of status epilepticus (see Chapter 6) in the NICU proceeds simultaneously on four fronts: termination of seizures; prevention of seizure recurrence once status is controlled; management of the precipitating causes; and management of the complications. Monitoring respiratory and cardiac function and continuous EEG monitoring is necessary in prolonged and refractory status. The appropriate titration of anaesthetic agents during status epilepticus may be based on the appearance of burst or, preferably, total suppression on the EEG. Continuous (or frequent, prolonged) EEG recording will give an indication of worsening or recurrence of status epilepticus regardless of the presence or absence of sedating drugs or paralysing agents. Indeed, electrographic seizure activity on the ICU may not be associated with any clear clinical manifestation or may be associated with only subtle signs such as nystagmus or hippus.

The complications of status epilepticus relate either to the cerebral and metabolic consequences of prolonged seizures or to the effects of medical treatment. Cardiopulmonary problems include the development of aspiration pneumonia, adult respiratory distress syndrome, pulmonary emboli, myocardial ischaemia and cardiac arrhythmia. Hyperthermia is common and rhabdomyolysis may develop. Prolonged hypoxia may cause cerebral damage and electrolyte disturbance, and metabolic acidosis may contribute to the development of multi-organ failure. Many drug treatments used in status epilepticus cause sedation, respiratory depression and hypotension. Artificial ventilation is required if general anaesthesia is indicated or if the seizures remain difficult to control. It is also necessary to maintain systemic blood pressure at normal or supra-normal levels to ensure adequate cerebral perfusion. Fluid resuscitation and/or inotropic support should be guided by appropriate cardiovascular monitoring.

Acute bacterial meningitis

The mortality and morbidity of acute meningitis in adults remain substantial, particularly if there is a delay in initiating treatment and monitoring of complications (Chapter 8). Patients with meningitis are usually admitted to an ICU when in coma, when there are complications such as seizures, cerebral oedema and tentorial herniation, or because they have developed systemic problems including septicaemia, pulmonary aspiration or cardiopulmonary compromise. Late deterioration following acute bacterial meningitis may be caused by antibiotic resistance or by the development of cerebral oedema, subdural effusion or empyema, superior sagittal sinus thrombosis, hydrocephalus, the development of focal neurological signs caused by an associated vasculitis, or systemic complications including pericardial effusion and polyarteritis.

Herpes simplex encephalitis

Clinical deterioration in this condion is usually the result of severe cerebral oedema with diencephalic herniation or systemic complications, including generalized sepsis and aspiration (Chapter 8). Furthermore, progressive worsening of focal seizures may lead to status epilepticus. The use of ICP monitoring in acute encephalitis remains controversial but should be considered if there is a rapid deterioration in the level of consciousness, and imaging suggests raised ICP. In this situation, aggressive treatment including tracheal intubation and mechanical ventilation with appropriate sedation should be instituted and seizures treated. Prolonged sedation or general anaesthesia may be necessary. Decompressive craniotomy may be successful in cases where there is rapid swelling of a non-dominant temporal lobe.

Neuromuscular disease

Patients with neuromuscular disease (Chapter 9) require NICU care when they develop acute or acute on chronic respiratory failure or acute bulbar or limb weakness. Patients with these disorders may develop severe and unexpected deterioration of respiratory, bulbar and limb function as a consequence of intercurrent events including systemic infection, disease exacerbation and increased pulmonary load, e.g. pregnancy or obesity.

Guillain–Barré syndrome

The indications for admission include ventilatory insufficiency, severe bulbar weakness threatening pulmonary aspiration, autonomic instability or coexisting general medical factors. Often, a combination of factors is present. The incidence of respiratory failure requiring mechanical ventilation in Guillain–Barré syndrome is approximately 30%. Ventilatory failure is primarily caused by inspiratory muscle weakness, although weakness of the abdominal and accessory muscles of respiration, retained airway secretions leading to pulmonary aspiration and atelectasis are all contributory factors. The associated bulbar weakness and autonomic instability reinforce the need for control of the airway and ventilation. Acute motor and sensory axonal neuropathy, the axonal form of Guillain–Barré syndrome, usually presents with a rapidly developing paralysis developing over hours and the rapid development of respiratory failure requiring tracheal intubation and ventilation. There may be total paralysis of all voluntary muscles of the body, including the cranial musculature, the ocular muscles and the pupils. Prolonged paralysis and incomplete recovery are more likely and prolonged ventilatory support may be necessary.

Myasthenia gravis

In myasthenia gravis admission to the NICU is indicated by the development of incipient ventilatory failure, progressive bulbar weakness leading to failure of airway protection or severe limb and truncal weakness causing extensive paralysis. Admission should be determined by the rate of progression, the presence of bulbar weakness and the clinical state of the patient rather than an absolute level of FVC alone. Respiratory failure often results from a myasthenic crisis (usually precipitated by infection, surgery or inadequate treatment), but may also more rarely be precipitated by a cholinergic crisis. The associated bulbar weakness predisposes to pulmonary aspiration and acute respiratory failure necessitating urgent tracheal intubation and ventilation. Patients with recent onset generalized myasthenia gravis started on a high-dose daily corticosteroid regimen are particularly at risk for acute paradoxical deterioration during the first 48–96 hours of treatment. Thymectomy should be coordinated by an NICU with experience of the procedure; postoperative management requires such experience.

Botulism

Botulism must be distinguished from Guillain–Barré syndrome and myasthenia gravis. Patients with acute bulbar and respiratory impairment require admission to the NICU and mechanical ventilation is often required. If patients survive the acute phase of illness, recovery is usually complete. Indeed, mortality in the era of the ICU is less than 10%.

Tetanus

Most patients with established tetanus will be admitted to an NICU because of increased muscle tone and spasms that typically begin in the masseter muscles, resulting in the classic finding of trismus. Respiratory compromise is caused by spasm of respiratory muscles or laryngospasm. Autonomic dysfunction occurs in severe cases and results in heart rate and blood pressure lability, arrhythmias, fever, profuse sweating, peripheral vasoconstriction and ileus. Muscle rupture and rhabdomyolysis can complicate extreme cases.

Supportive care consists of treatment in a quiet ICU setting to allow cardiorespiratory monitoring with minimal stimulation. Therapeutic paralysis with neuromuscular blocking agents may be necessary in severe cases. Intubation may be required owing to hypoventilation caused by muscular rigidity or laryngospasm and should be performed in a controlled elective manner if possible. Treatment in the ICU has resulted in a pronounced improvement in prognosis for patients with tetanus. Modern mortality is approximately 10%.

General medical care on the neuromedical intensive care unit

The role of an intensive care unit is to maintain a patient's normal physiological homeostasis while actively treating the underlying cause of any physiological derangement. The following general medical complications may arise during the care of patients on an NICU.

Pulmonary complications

The most frequent manifestations are acute hypoxaemic respiratory failure caused by ventilation–perfusion mismatch from infection (often secondary to aspiration), atelectasis, pulmonary oedema or pulmonary embolus.

Nosocomial or aspiration pneumonia

This is usually caused by gastric and oesophageal colonization with aerobic bacteria and repeated small volume aspiration during sleep. It usually develops subclinically and fulminant aspiration syndrome is rare. Intensive physiotherapy and nursing support are essential, and mechanical ventilation may be indicated if progressive infiltration abnormalities are shown. Appropriate broad-spectrum empirical antibiotic treatment with a cephalosporin and metronidazole are indicated.

Ventilator-associated pneumonia

This may develop after intubation and is caused by retrograde colonization of the oropharynx caused by gastro-oesophageal reflux and possibly compounded by cross-colonization from other patients, hospital personnel or equipment. It is frequently caused by *Pseudomonas aeruginosa* infection.

Acute lung injury and acute respiratory distress syndrome

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are the most severe form of acute lung disturbance and are characterized by inflammation and increased permeability of lung tissue associated with a variety of clinical, radiological and physiological abnormalities that cannot be explained by a primary cardiac cause. They may be associated with a wide range of conditions including sepsis, trauma, aspiration pneumonitis and fat embolism. They result in reduced pulmonary compliance, arterial hypoxaemia resistant to oxygen therapy and bilateral infiltrates on chest X-ray. They often lead to multi-organ failure and have a high mortality.

Management is largely supportive with the use of sophisticated artificial ventilation strategies while ensuring adequate nutrition, deep vein thrombosis (DVT) prophylaxis and prevention of infection. The management of ARDS calls for permissive hypercapnia (with low tidal volumes) to help reduce pressure in airways; in cases with intracranial mass lesions with risk of ICP elevation or herniation, this therapy may have serious deleterious consequences.

Neurogenic pulmonary oedema and pulmonary emboli

Neurogenic pulmonary oedema may develop after an acute injury to the brain or brainstem in patients with intracranial pathology, including subarachnoid haemorrhage, cerebral emboli, cerebral tumours, status epilepticus and raised ICP. Chest X-ray shows diffuse pulmonary infiltrates, but the diagnosis depends on showing hypoxaemic respiratory failure with a normal pulmonary artery wedge pressure in the absence of a cardiac cause. The presentation of pulmonary embolism is often variable and pulmonary emboli may be silent and difficult to diagnose. Smaller emboli may cause few haemodynamic effects or may result in infarction of a section of lung tissue if collateral blood flow is inadequate. Massive pulmonary emboli cause rapid respiratory and cardiovascular collapse and death.

Cardiovascular system

The principal function of monitoring the cardiovascular system in NICU is the maintenance of arterial blood pressure and blood volume to ensure adequate organ perfusion.

Hypotension

Hypotension may be the result of an inadequate circulating blood volume, poor myocardial contractility, a decreased systemic vascular resistance (SVR) or a combination of these factors.

Hypovolaemia

Hypovolaemia is common and the choice of fluid replacement depends on a number of factors. If the patient is anaemic (haemoglobin <8 g/dL), transfusion of red cells should be considered, especially if the patient has a history of ischaemic heart disease. If the patient's haemoglobin is above this value, blood volume may be increased by the use of colloid or crystalloid solutions. Generally, in neurointensive care practice, 0.9% sodium chloride solution is favoured over glucose or lactate containing solutions which have the potential to increase intracellular glucose concentrations and thus increase the risk of ischaemic damage. The use of 0.9% NaCl solution is necessary to maintain isotonicity; use of hypotonic solutions may precipitate cerebral swelling leading to increased ICP and herniation.

Decreased myocardial contractility

Decreased myocardial contractility may be the result of many factors including ischaemic heart disease, sepsis, hypoxaemia, hypercarbia, acidosis, cardiac disease, electrolyte disturbance and drugs (e.g. most intravenous anaesthetic agents used for sedation of patients on NICU). Inotropic drugs such as noradrenaline (norepinephrine), adrenaline (epinephrine) and dobutamine are used to improve contractility and therefore cardiac output.

Hypertension

Hypertension is a common consequence of acute neurological events and its treatment requires careful consideration. A high MAP may predispose to rebleeding after subarachnoid haemorrhage, worsening of cerebral oedema, extension of haemorrhage or haemorrhagic transformation of an infarct. However, it may be detrimental to attempt to control acute hypertension because patients with raised ICP require an elevated MAP to maintain an adequate cerebral perfusion pressure, and any fall in cerebral blood flow may lead to global ischaemia. If treatment is necessary, commonly used drugs in the acute situation include intravenous labetalol, hydralazine and sodium nitroprusside, although the latter is reported to increase intracranial pressure.

Arrhythmias

Cardiac arrhythmias are associated with aneurysmal SAH, head injury, acute ischaemic or haemorrhagic stroke, status epilepticus, Guillain–Barré syndrome and impending or established brain death. The most common morphological ECG changes in acute CNS events are often self-limiting and treatment is not indicated.

Sinus bradycardia is associated with sympathetic blockade and/or increased vagal tone. It occurs in Guillain–Barré syndrome. It is an indication of potential heart block and cardiac arrest. It may be treated with anticholinergic drugs (e.g. atropine), β-adrenergic receptor agonists or cardiac pacing. Sinus tachycardia is extremely common in acute neurological illness and may be associated with hypoxaemia, hypercapnia and neuromuscular blockade or as a compensatory mechanism in anaemia, hypovolaemia and pulmonary emboli. Treatment is usually directed at the cause. β-Adrenergic receptor blockers may be required if the patient is at risk of myocardial ischaemia. Atrial fibrillation with a rapid ventricular response is common, as either a cause or a consequence, in acute stroke. Drug treatment is aimed at reducing atrioventricular node conduction and ventricular rate. Digoxin may be used, but β-blockers, verapamil and amiodarone are also valuable and DC cardioversion may be necessary if blood pressure is compromised. Atrial flutter may compromise ventricular filling and increase the risk of ischaemia. The treatment is aimed at restoring sinus rhythm using DC cardioversion or antiarrhythmic drugs. Heart block is most commonly seen in Guillain–Barré syndrome and cardiac pacing may be necessary as there can be rapid progression to cardiac arrest. Ventricular tachycardia is common in SAH and may predispose to the development of torsade de pointes, ventricular flutter and ventricular fibrillation. Antiarrhythmic drugs may be needed, but immediate electrical cardioversion is indicated if resistant ventricular tachycardia causes hypotension.

Hyponatraemia

Hyponatraemia is defined as serum sodium level ≤135 mmol/L. The causes of hyponatraemia are classified according to the extracellular fluid osmolality, intravascular volume and pressure status. Normal serum osmolality (2[Na^+] + urea + glucose [mmol/L]) is in the range of 285–295 mOsm/kg.

Hypertonic hyponatraemia is caused by the presence of osmotically active solutes other than sodium (e.g. glucose and mannitol), which lead to shifts of free water from the intracellular to the extracellular component. Normotonic hyponatraemia is usually caused by retention of large volumes of isotonic solutes that dilute sodium (e.g. hyperlipidaemia). Hypotonic hyponatraemia (serum osmolality <260 mOsm/kg) is by far the most common abnormality seen in neurological patients. It occurs when there is excessive water retention in relation to Na^+ and may be classified according to the volume state of the patient. Hypervolaemic hypotonic hyponatraemia is associated with excessive body fluid load as may be seen with cirrhosis, acites, congestive cardiac failure, nephrotic syndrome and severe hypoproteinaemia. Hypovolaemic hypotonic hyponatraemia is caused by excessive extrarenal loss (e.g. diarrhoea, vomiting, sweating, pancreatitis, burns) or renal loss (e.g. use of diuretics or as occurs in renal failure).

Inappropriate secretion of ADH

In normovolaemic hypotonic hyponatraemia there is excessive water retention by the kidneys leading to dilutional hyponatraemia with mild expansion of the extracellular fluid. The condition is usually caused by inappropriate secretion of ADH (SIADH), which occurs when ADH is not appropriately suppressed by low plasma osmolality. This leads to further reabsorption of free water in the distal renal tubules; however, in SIADH sodium handling remains unaffected so that there is a paradoxical increase in sodium excretion attempting to return the intravascular volume to normal levels. Therefore, increased urinary sodium excretion continues despite the increase in free water. The features of SIADH are summarized in Table 19.16.

Inappropriate ADH secretion is associated with a variety of neurological and systemic causes summarized in Table 19.17.

Table 19.16 Criteria for the diagnosis of syndrome of inappropriate ADH secretion.

Hyponatraemia (serum $Na^+ \leq 135$ mOsm/L)
Plasma hypotonicity (plasma osmolality <280 mmol/kg)
Inappropriately concentrated urine (osmolality >100 mL/kg)
Continued sodium excretion (urinary $Na^+ > 20$ mOsm/L)
The patient being clinically normovolaemic
Exclusion of cardiac, renal or endocrine disease

Table 19.17 Causes of syndrome of inappropriate ADH secretion.

Neurological disorders
Head injury, trauma
Cerebrovascular – infarction, ICH, SAH
Tumours
Abscess, meningitis, encephalitis
Guillain–Barré syndrome, acute intermittent porphyria
Pulmonary disorders – pneumonia, TB, COPD, asthma
Malignancy – bronchus, lymphoma, prostate, pancreas
Endocrine – hypothyroidism, Addison's disease
Drugs
Analgesics – NSAIDs, opiates
Antiepileptics – carbamazepine
Antidepressants – SSRIs, tricyclics, monoamine oxidase inhibitors
Chemotherapy agents – vincristine, vinblastine, cyclophosphamide
Antipsychotics – haloperidol, thioridazine
Hypoglycaemic agents – chlopropamide, tolbutamide
Postoperative

COPD, chronic obstructive pulmonary disease; ICH, intracerebral haematoma; NSAID, non-steroidal anti-inflammatory drug; SAH, subarachnoid haemorrhage; SSRI, selective serotonin re-uptake inhibitor; TB, tuberculosis.

Cerebral salt wasting

Hypovolaemic hyponatraemia may also occur in association with the condition of cerebral salt wasting (CSW). In this condition a centrally mediated process leads to increased sodium and water excretion and hypovolaemia, in contrast to SIADH which is characterized by excessive sodium loss with water retention by the kidneys. In clinical practice the only reliable way of distinguishing SIADH and CSW is assessment of the volume status. Hypovolaemia, as seen in CSW, is associated with orthostatic hypotension, tachycardia, dry mucous membranes, poor skin turgor and reduced central venous pressure but none of these signs is entirely reliable.

The distinction between SIADH and CSW is essential because the management of SIADH involves reduction in the intake of electrolyte-free water to reduce the expansion of intracellular volume. The administration of saline would simply increase the extracellular fluid as sodium continues to be lost as a consequence of ongoing ADH secretion and the shift of sodium from the extracellular fluid to the intracellular fluid would cause progressive cerebral oedema. Conversely, in CSW, where there is a hypovolaemic state, treatment is the administration of isotonic or hypertonic saline to counteract the primary abnormality of renal salt wasting. In this situation, fluid restriction actually worsens the hypovolaemia and hyponatraemia as the salt wasting continues. The situation is particularly complex in SAH where there appear to be features of both SIADH and CSW. However, the hypovolaemic state exacerbates vascular spasm and therefore it is now widely accepted that hypervolaemic therapy is appropriate to prevent further vascular spasm.

In general clinical practice, acute symptomatic hyponatraemia is often brought about by hypervolaemic states such that occur in congestive cardiac failure or nephrotic syndrome and treatment is therefore with loop diuretics to promote renal loss of water in excess of sodium. Treatment of asymptomatic hyponatraemia should be cautious with mild free water restriction if the patient is isovolaemic or hypovolaemic.

Central pontine myelinolysis

Central pontine myelinolysis is a demyelinating syndrome, initially described in alcohol or malnourished patients. The condition is associated with rapid correction of hyponatraemia which leads to shift of fluid from the intracellular to the extracellular compartments causing dehydration of the brain resulting in non-inflammatory damage to the myelin sheath and the oligodendrocytes with relative sparing of neurones and axons.

The condition may present with a severe and unexplained encephalopathy or seizures occurring secondary to hyponatraemia but it may progress to flaccid quadriparesis, pseudobulbar palsy manifest as dysarthria, dysphagia with pupillary and oculomotor abnormalities and occasionally patients may present with a locked-in syndrome. The presence of extrapontine myelinolysis leads to a more diffuse neurological pattern with movement disorders including parkinsonism, choreoathetosis, dystonia and spasmodic dysphonia.

Demyelination is most frequently seen in the central pons, but may extend into the midbrain; however, extrapontine myelinolysis is often symmetrical and may occur in the cerebral cortex, external capsule, limbic system or basal ganglia. MRI confirms the presence of hyper-intense lesions on T2-weighted images, which do not enhance and are seen primarily in the central pons. Diffusion-weighted imaging is a more sensitive technique to show these abnormalities.

The outcome is variable and the prognosis depends on the severity and extent of demyelination in the pons. Some patients may recover from the condition despite extensive radiological or clinical involvement.

Alimentary system

Protein catabolism is almost invariable in patients nursed on the ICU and is often caused by an inadequate supply of calories and an increased energy and oxygen consumption associated with the stress response to injury and sepsis. The resultant generalized muscle loss also affects respiratory muscles and may contribute to difficulties in weaning from mechanical ventilation.

Enteral feeding via a nasogastric tube should be started as soon as possible as this decreases catabolism, provides protection against peptic ulceration and maintains intestinal integrity, thus decreasing the occurrence of bacterial translocation (see nosocomial infection). Adynamic ileus is common and often requires the use of prokinetic agents such as metoclopramide or erythromycin. Total parenteral nutrition should only be used if enteral nutrition fails or is not possible, usually because of ileus. Gastrointestinal bleeding is common in NICU patients, but is usually minor and manifests as chronic anaemia in the presence of positive faecal occult blood. The routine use of H_2 receptor antagonists (e.g. ranitidine) or proton pump inhibitors should be avoided as they increase the incidence of nosocomial infection.

Constipation occurs as a result of opioid drug administration, immobility and a lack of fibre in some enteral feeds. Treatment with oral or rectal laxatives is usually necessary. Diarrhoea has many causes but infection (including that by *Clostridium difficile*), malabsorbtion and diarrhoea associated with enteral feeds are the most important.

Nosocomial infection and infection surveillance

Sepsis (and the systemic inflammatory response to sepsis) remains the major cause of organ failure and death in the ICU, being either directly or indirectly responsible for 75% of all deaths. Common sites of infection include the urinary tract, respiratory tract (especially ventilator-associated pneumonia) and vascular cannulae (catheter-related sepsis), which is particularly associated with internal jugular and subclavian catheters, but peripheral catheters also carry a considerable risk. Thus, placement of intravenous catheters requires meticulous aseptic technique and regular changing of lines. It is important to ensure that the tips of catheters that have been removed are sent for culture. Catheter-related infections are usually caused by coagulase-negative staphylococci (*Staphylococcus epidermidis* or *S. aureus*) and treatment should be directed by sensitivities determined by culture.

The importance of infection control in the NICU cannot be overstated. This involves the isolation of the infected patient whenever possible, meticulous staff hygiene (e.g. hand-washing before and after each patient contact, aseptic techniques for invasive procedures), early identification and treatment of infection by the routine sending of blood, urine, sputum for culture, use of disposable equipment and, most importantly, joint daily ward rounds between microbiologists and the ICU team (Table 19.18).

Table 19.18 Risk factors for nosocomial infections.

Age over 70
Widespread use of broad-spectrum antibacterial drugs
Mechanical ventilation and endotracheal tube
Presence of foreign bodies (e.g. intravascular cannulae, bladder catheter, pacemaker)
Immunodeficiency states and immunosuppressant medication
Colonization of the oropharynx
Use of H_2 receptor antagonists
Underlying chronic lung disease and reintubation

Anticoagulation

Prophylaxis against venous thrombosis is essential and all patients should wear graduated compression stockings and have regular active or passive leg exercises. Unless contraindicated, low molecular weight heparin should be routinely administered.

Table 19.19 Causes of agitation and restlessness on the neurological intensive care unit (NICU).

Pain
Anxiety
Confusion
Sleep deprivation
Sepsis
Drugs
Drug withdrawal
Metabolic (hypoglycaemia, hyperglycaemia, hyponatraemia, uraemia, hepatic)
Respiratory (infection, hypoxaemia, hypercarbia)
Cardiac (low output state, hypotension)

Patient comfort

Agitation is common in the NICU and has a variety of causes (Table 19.19). It may manifest as discomfort, pulling at intravenous and bladder catheters, tracheal and nasogastric tubes, shouting, aggressive behaviour, extreme restlessness and confusion. Pain is particularly common and often unrecognized because of confusion and the difficulties with communication in the aphonic or paralysed patient.

Many patients require sedation but there is a natural reluctance to sedate patients with an evolving CNS disorder. The first line of management is to reassure and calm the patient in a quiet environment and to ensure a normal diurnal cycle. There should be careful nursing and treatment of the underlying causes, including positioning, splinting, bed cages, catheterization and physical treatments. None the less, sedative and analgesic drugs are often necessary to reduce distress, anxiety and pain and to aid toleration of tracheal tubes, intermittent positive pressure ventilation (IPPV), tracheal suction and physiotherapy.

Propofol, a di-isopropylphenol, is extensively used for short-term sedation of critically ill adult patients. Its pharmacokinetic properties allow rapid wakening after discontinuation of its infusion, even in patients with poor renal or hepatic function. Its use may result in hypotension which may require the introduction of inotropic agents such as noradrenaline. Benzodiazepines have been extensively used in the ICU setting; water-soluble midazolam is the drug of choice as it is metabolized to inactive compounds and has a shorter half-life (2 hours) than other members of the group and has an amnesic effect. Total doses of propofol or midazolam can be reduced by the concomitant use of opioid drugs such as fentanyl and morphine. The use of such sedative and opioid drugs often allows mechanical ventilation without having to resort to neuromuscular blocking drugs.

Pain

Pain is a prominent feature of many neurological conditions seen in the NICU and needs to be recognized and treated effectively, particularly in patients with a reduced level of consciousness or who are mechanically ventilated and not able to communicate. In the latter situation pain is frequent and may be severe, it must be distinguished from confusion or agitation. Combinations of opioid and non-opioid drug treatment, including agents directed towards neuropathic pain (e.g. amitriptyline, gabapentin) may be required. Opioid analgesics are commonly used in the NICU. These provide effective analgesia, induce euphoria and aid toleration of IPPV. Side effects of opiates include hypotension, respiratory depression, nausea and vomiting, and decreased gut motility; the fear of addiction is vastly exaggerated. Intravenous administration is more easily controlled and predictable. Commonly used drugs include morphine and fentanyl but short-acting drugs such as remifentanil may be valuable. Non-opioid analgesics include paracetamol and other non-steroidal anti-inflammatory drugs such as diclofenac; these are increasingly used in the NICU as they have a minimal effect on the level of consciousness. The most important side effect is gastric toxicity. Codeine is an alternative, weaker analgesic.

Communication

Speech is often possible even in patients who are mechanically ventilated via a tracheostomy. It requires specialist speaking valves and, more importantly, the expertise of an experienced speech and language therapist. Where speech is impossible, other communication aids should be used.

Sleep

Sleep deprivation almost invariably occurs in patients nursed in an ICU setting. Factors include disruption of day–night cycles, environmental factors such as noise and patient factors such as fear. The disruption is associated with agitation, confusion and the development of ICU psychosis. Furthermore, sleep deprivation has a direct effect on respiratory muscle function, catabolism and the immune response. It is essential to re-establish a normal pattern of sleep by the use of hypnotic drugs (e.g. benzodiazepines, sedative tricyclic antidepressants, zopiclone). The use of melatonin has proved useful in resistant insomnia.

Communication with the family

Communication with family and friends on the ICU presents great challenges for medical and nursing staff. It is essential that staff should be consistent in their assessment and honest in the appraisal of the uncertainties in management and prognosis. It is preferable if only one or two clinicians act as the primary source of information. It is important to recognize that the family may experience acute stress reactions which may be manifest as anger, frustration, bitterness and guilt. There must be adequate and patient discussion, often on a daily basis. While patients are insentient as a consequence of the disease or its treatment the family are their advocate. Frequently, families are involved in end-of-life decisions for comatose patients in whom there is no hope of recovery. It is essential to establish, if possible, the patient's own preference for management through living wills, advanced directives or simply by having voiced a clear preference to family or the surrogate decision-makers. The autonomy of the patient must be maintained by respecting these preferences, although a consensus agreement of family members must always be sought by careful explanation and education.

Neurology of general critical care

The majority of neurologists work in district general or teaching hospitals with large general ICUs. In this setting, ICUs require an increasing input from neurologists, especially with regard to the assessment of hypoxic brain damage and the neurological complications of organ failure, critical illness and sepsis.

Neurological complications on the ICU are usually caused by metabolic encephalopathy, seizures, hypoxic-ischaemic encephalopathy, stroke or neuromuscular disorders but multiple complications are common.

Sepsis

The sepsis syndromes represent a spectrum of clinical illness including the systemic inflammatory response syndrome (SIRS), single organ dysfunction, multiple organ failure and death caused by immune responses to infection. SIRS is a severe systemic response that occurs in up to 50% of those in a critical care setting in response to infection or other insults, such as burns, trauma or surgery. In addition to the initial insult, the clinical features of this syndrome are two or more of the following: temperature >38°C or <36°C, heart rate >90, respiratory rate >20 or $PaCO_2$ <32 mmHg, and white blood cell count >12,000 or <4000 cells/mm^3. Septic shock occurs if sepsis is associated with hypotension despite adequate resuscitation (intravenous fluids, inotropes, vasoactive agents and specific treatment). Multiple organ dysfunction syndrome (MODS) or multiple organ system failure is defined as the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

Failure to awaken/depressed conscious state

Sudden or gradual deterioration in consciousness may occur during an ICU stay or reflect failure to awaken after general anaesthesia for several reasons (Table 19.20). Sedation and analgesia are confounding factors in those with depressed consciousness.

Table 19.20 Causes of failure to awaken on ICU after sedation or anaesthetic.

Drugs – sedation, analgesia, neuromuscular paralysis
Hypoxic – ischaemic injury
Sepsis
Metabolic encephalopathy – renal, hepatic, electrolyte, endocrine
Stroke
Primary CNS inflammation
Multi-factorial – most common

These drugs are used to reduce agitation and pain, with the goals of diminishing discomfort, oxygen demand, ventilator asynchrony and self-removal of catheters and other devices. They also induce amnesia and reduce the risk of a post-traumatic stress disorder. Withdrawal of sedation before review is essential for reliable neurological assessment. It will also eliminate the temptation to attribute depressed consciousness to sedation alone. The choice of sedative drugs must be carefully considered especially in relation to their half-lives and potential interactions.

Encephalopathy

If prolonged sedation has been excluded, the most common cause of depressed consciousness is a metabolic encephalopathy which may be a result of one or more causes (Table 19.19). The diagnosis may be difficult in an unconscious patient and careful assessment of medication, sepsis, metabolic status and fluid balance is essential.

Septic encephalopathy

Septic encephalopathy is the most common form of encephalopathy encountered in intensive care medicine and is present in 50–70% of septic patients. It is characterized by disorientation, delirium, impaired consciousness or coma. There may be rigidity, tremors and seizures. Usually, an extracranial site of infection can be identified and appropriate treatment commenced, but in <50% of septic encephalopathy cases is an organism isolated from blood cultures. EEG is a sensitive diagnostic investigation for septic encephalopathy; the findings lack specificity but correlate well with the severity of encephalopathy and mortality.

The pathogenesis of septic encephalopathy is likely to be multifactorial and may include bacterial toxin release, high fever and as an effect of mediators of inflammation (such as interferon-α, interleukin-1β or tumour necrosis factor α). The outcome attributable to septic encephalopathy is difficult to separate from the outcome related to the precipitating condition and coexisting renal and hepatic impairment. The sepsis syndromes resulting in septic encephalopathy independently have high morbidity and mortality; however, the condition is potentially reversible so the aims of treatment are removal of the underlying source of sepsis and supportive intensive care.

Uraemic encephalopathy

Uraemic encephalopathy can occur as a consequence of renal failure but a similar clinical pattern can also develop as a result of treatment in dialysis dementia and the dialysis disequilibrium syndrome, although these conditions are now extremely rare. Clinical features of uraemic encephalopathy are non-specific with fatigue, insomnia, pruritus and progressive cognitive impairment culminating in asterixis, tetany, myoclonus, confusion, seizures, stupor and coma. Progression mirrors the severity of uraemia although coexisting metabolic and endocrine factors may also be present (e.g. hypocalcaemia, hyperphosphotaemia, hypokalaemia and metabolic acidosis). Uraemic encephalopathy is easily reversible with dialysis or transplantation. Dialysis disequilibrium syndrome generally follows the initiation of treatment with haemodialysis and is probably caused by the development of cerebral oedema. It may be associated with milder manifestations including disorientation, tremor or more severe features including seizures and coma.

Hepatic encephalopathy

Hepatic encephalopathy presents with lethargy, somnolence and disorientation leading to coma associated with a flapping tremor (asterixis) and foetor. Features of raised ICP and seizures may occur before the development of deep coma. There are no specific diagnostic liver function test abnormalities although elevated blood ammonia levels and an abnormal EEG (bilateral synchronous delta waves and triphasic waves) indicate hepatic encephalopathy. Severe acute hepatic encephalopathy is an ICU emergency involving the management of acute elevated ICP and requiring monitoring, ventilation and mannitol. Hypothermia and hyperbaric oxygen have also been used. The management of chronic hepatic encephalopathy requires avoidance of precipitating factors, lactulose and antibiotics, particularly neomycin. Fulminant hepatic failure leads to cerebral oedema, whereas chronic hepatic encephalopathy is caused by accumulation of substances secondary to liver failure and portal–systemic shunting. Mannitol, hyperventilation and high dose barbiturates may be useful in acute encephalopathy but steroids and haemofiltration are ineffective.

Anoxic–ischaemic encephalopathy

Neurologists are frequently asked to assess the prognosis of patients who have sustained hypoxic brain injury secondary to cardiac arrest or severe hypotension during cardiac surgery. The importance of establishing an early prognosis is to guide managements and, in particular, to determine the appropriate level of support and the possibility of recovery or prolonged survival in a profoundly disabled state. Hypoxic-ischaemic injury usually follows cardiac arrest and carries a very poor prognosis. The history of the event and the presence of pre-arrest morbidity are important prognostic factors but detailed examination of the patient, as described above, remains the mainstay of assessment.

Central pontine myelinolysis

With central pontine myelinolysis (see above and Chapter 18), rapid changes in plasma sodium and osmolarity produce on imaging the typical ‘bat wing’ appearance of pontine demyelination (Figure 19.14). Demyelination can be predominantly extra-pontine (25%). Presentation is with impaired conscious level, brainstem signs and limb weakness.

Reversible posterior leucoencephalopathy

This condition occurs as a result of acute hypertensive encephalopathy, eclampsia or immunosuppression. The onset is with headache, vomiting and a progressive encephalopathy characterized by confusion and disorientation. There may be seizures and visual disturbance, in particular cortical blindness. The condition is associated with immunosuppressive therapy particularly after transplantation using ciclosporin, cisplatinum, 5-fluouracil, amphotericin B, methotrexate, tacrolimus or interferon-α. It is also seen in eclampsia and acute hypertensive encephalopathy associated with renal disease. Reversible posterior leucoencephalopathy seems to arise from a mechanical disruption of the blood–brain barrier, either by overwhelming hydrostatic factors, e.g. hypertension, or dysfunction of the endothelial cells of the barrier because of toxins. The MRI shows characteristic high intensity white matter abnormalities on T2-weighted sequences in the parieto-occipital white matter. Fluid attenuated inversion recovery (FLAIR) sequences show a similar predominantly white matter pattern of hyperintensity consistent with vasogenic oedema (Figure 19.15). In general, changes are confined to the

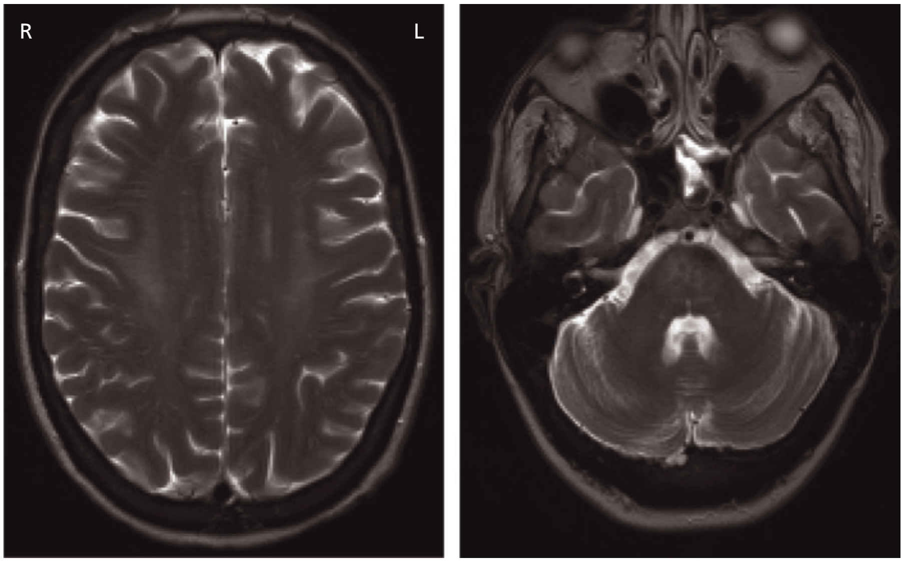
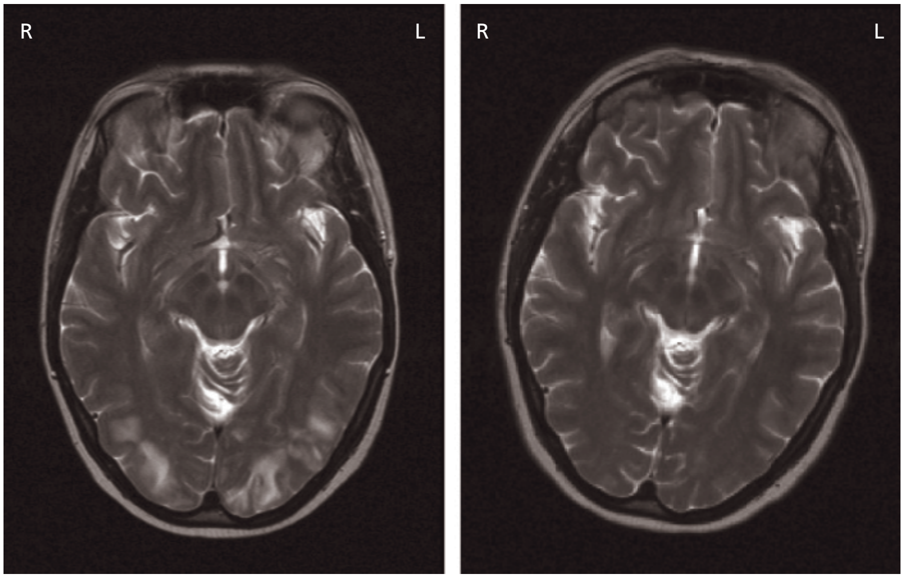


Figure 19.14 Central pontine myelinolysis showing extensive pontine and extrapontine demyelination (MRI T2W).



(a)

(b)

Figure 19.15 Posterior reversible leucoencephalopathy in a patient who was hypertensive following the administration of intrathecal methotrexate. MRI T2W: (a) following intrathecal methotrexate; and (b) 3 months later showing complete resolution. (Scans courtesy of Dr Paul Holmes, St. Thomas’ Hospital.)

posterior circulation territory. It is suggested this is because the vascular blood in this area has lower pressure and less sympathetic innervation compared to the anterior circulation and is therefore more easily affected by systemic hypertension. However, there are increasing reports of anterior territory or asymmetrical changes occurring. Management is with antihypertensive agents, withdrawal of immunosuppression and supportive care. This condition is reversible with treatment and the MRI scan may normalize but there may be residual focal cerebral haemorrhage or permanent injury.

Seizures

Seizures on the ICU are usually focal or generalized motor convulsions, although all seizure types occur. Common precipitants are hypoxia-ischaemia, drug toxicity, narcotic withdrawal and metabolic abnormalities (Table 19.21). It is essential to diagnose the seizure type and cause to ensure early appropriate treatment and differentiation from metabolic myoclonus and extrapyramidal movement disorders. Non-convulsive status epilepticus is common and a poorly recognized cause of coma. Classic ictal signs may be absent and diagnosis may depend on the observation of subtle movements of fingers, eyes or lips. Non-convulsive status epilepticus should be considered where there is abrupt deterioration in conscious level without explanation, often following a recognized seizure or after anoxic ischaemic insult with preserved brainstem reflexes. Convulsive status is less common. EEG monitoring may be helpful.

Myoclonic status

Myoclonic status occurs within 12 hours of cardiac resuscitation and persists for a further 48 hours. These patients are deeply unconscious with jerking movements involving limbs and face (grimacing and eye opening) which are typically unresponsive to drug treatment. Myoclonic status is a poor prognostic sign predicting death or vegetative state in 90% of cases. Absolute prognostication is difficult, as is the decision to maintain life support. SSEPs may help but are not always available. The severity of imaging findings usually guides decision-making.

Table 19.21 Causes of partial or generalized status epilepticus.

Acute
Head injury
CNS infection (encephalitis, meningitis)
Cerebrovascular accident
Renal failure
Sepsis syndrome
Drug toxicity
Electrolyte imbalance
Hypoglycaemia
Hypoxic – ischaemic brain injury
Pseudostatus
Benzodiazepine or other suppressant withdrawal
Chronic
Pre-existing epilepsy
Poor antiepilepsy drug compliance
Dosage alteration
Chronic alcoholism/alcohol withdrawal
Cerebral space-occupying lesion

Lance–Adams syndrome

The Lance–Adams syndrome (post-anoxic action myoclonus) is seen after hypoxic brain injury, especially following cardiac resuscitation. Myoclonic jerks become evident as consciousness is regained and a favourable response to benzodiazepines, piracetam or valproic acid is usual.

Weakness and failure to wean from mechanical ventilation

Weakness on the ICU often presents as difficulty in weaning from ventilation but there may also be reduced movements in an obtunded patient, or generalized or focal weakness in an alert patient. This must be distinguished from the non-specific weakness of fatigue secondary to systemic illness.

Weakness may be central or peripheral. In the comatose patient, a central cause should be suspected if there are upper motor neurone signs, if the distribution of the weakness is pyramidal or if there is a hemiparesis. Paraparesis is often caused by nerve or muscle disorders, and less often spinal disorders (infarction secondary to a hypotensive or embolic episode). Monoparesis may occasionally be a manifestation of a stroke but more often a consequence of pressure or positioning palsy (femoral or common peroneal nerve palsies).

Neuromuscular disease may occur in the ICU patient as:

- A complication of a non-neurological illness (e.g. critical illness polyneuropathy associated with SIRS);
- A primary neurological disorder (e.g. Guillain–Barré syndrome);
- An acute exacerbation of an underlying neuromuscular condition (e.g. myasthenia gravis);
- Progression of a previously diagnosed neuromuscular disease (e.g. Duchenne muscular dystrophy, motor neurone disease, acid maltase deficiency); or
- A complication of treatment (e.g. acute quadriplegic myopathy).

Neuropathies

The ICU patient is at risk of developing neuromuscular complications of prolonged ICU care. The most common is critical illness polyneuropathy (CIP); however, other causes such as therapeutic agents and nutritional deficiency must be considered. Guillain–Barré syndrome, acute motor axonal neuropathy and acute intermittent porphyria are rare in patients already receiving intensive care but must be considered.

Critical illness polyneuropathy

CIP is an acute sensorimotor axonal neuropathy that develops in the setting of SIRS and/or multi-organ failure, particularly in the presence of hypoalbuminaemia, hyperglycaemia and insulin deficiency. Up to 70% of patients with sepsis and multi-organ failure develop abnormalities on nerve conduction studies. CIP is characterized by delayed weaning, severe flaccid wasting and weakness, areflexia and sensory impairment may be seen in patients who are able to cooperate with the examination. However, the signs are variable and difficult to elicit because of sedation or coexistent septic encephalopathy. CIP is self-limiting but the overall prognosis is influenced by the severity of the underlying condition and this accounts for the majority of mortality in the condition. Recovery may be rapid and complete but a significant proportion of patients with severe neuropathy, requiring axonal regeneration for recovery, either have no recovery or a persistent deficit. Recognition of CIP is important as it may guide ventilatory management and indicate that prolonged care in the critical care unit may be necessary. The earliest electrophysiological sign of CIP is a reduction of compound muscle action potential amplitudes with reduction in the amplitude of the sensory nerve action potentials. Fibrillation potentials and positive sharp waves may not appear in muscle until 3 weeks. Nerve biopsy and autopsy studies show axonal degeneration of both sensory and motor fibres without evidence of significant inflammation or primary demyelination. It has been suggested that the condition may be prevented by tight control of glucose levels. The pathophysiology of CIP is uncertain but in the setting of SIRS, humoral and cellular mechanisms are initiated that disturb microcirculation, leading to inadequate perfusion of the peripheral nerves.

Muscle disease

Muscle disease on the ICU may occur as a consequence of prolonged neuromuscular junction blockade or direct myopathic involvement.

Neuromuscular junction blocking agents

Neuromuscular junction blocking agents (NMBA) are used increasingly to facilitate intubation, improve lung compliance, allow more efficient mechanical ventilation and reduce fluctuations in ICP.

Suxamethonium is a short-acting neuromuscular blocking agent that produces intense neuromuscular relaxation by causing prolonged depolarization of the post-synaptic receptors at the neuromuscular junction. Its sole use is to effect tracheal intubation. Its duration of action lasts 2–5 minutes. It should be avoided in neurological disease as hyperkalemia may follow its use. In contrast, non-depolarizing NMBAs (e.g. atracurium, vecuronium) produce a longer lasting neuromuscular blockade by reversibly occupying post-synaptic receptors and antagonizing acetylcholine. They may be used to allow effective mechanical ventilation and in the management of critically raised ICP.

Prolonged neuromuscular blockade

Prolonged neuromuscular blockade after either short- or long-term blockade with non-depolarizing NMBAs may associated with metabolic acidosis, hepatic or renal insufficiency and elevated levels of magnesium. Weakness should not persist beyond 2 weeks after stopping the blocking agent and typically lasts for only a few days. Prolonged blockade should be considered in any patient who remains weak after discontinuation of NMBAs. The condition occurs in the context of cumulative doses of NMBAs often given with corticosteroids, aminoglycosides or other anaesthetic agents. Repetitive nerve stimulation is abnormal with a decremental response in the compound muscle potential amplitude but the creatine kinase (CK) levels are normal. Recovery usually occurs within several days after discontinuation of the NMBA. Other neuromuscular transmission disorders that may require admission to an ICU include organophosphate poisoning, botulism, tick paralysis, black widow spider and certain types of snake envenomation.

Neuromuscular disorders resulting from the disruption of neuromuscular transmission should be considered as a cause for neuromuscular weakness and failure to wean in critically ill patients. Neuromuscular disease can be unmasked in previously undiagnosed cases by medications commonly used intra-operatively and in the recovery room or ICU. Patients with myasthenia gravis or the Lambert–Eaton myasthenic syndrome have an extremely high sensitivity to even low doses of neuromuscular blocking drugs and other agents such as aminoglycoside antibiotics and certain antiarrhythmic agents that have little effect on neuromuscular transmission in healthy people.

Non-necrotic cachectic myopathy

Non-necrotic cachectic myopathy is common and is manifest as muscle wasting with associated weakness. The electromyogram (EMG) and CK levels are normal.

Myopathy with selective loss of thick filaments (myosin) / Acute quadriplegic myopathy (AQM)

This condition is associated with exposure to high doses of glucocorticoids and non-depolarizing muscle blocking agents (e.g. pancuronium, vecuronium or atracurium). AQM can occur in other situations including major organ transplantation, particularly liver. AQM does not seem to correlate with the duration of intensive care. Patients may present as the acute illness resolves when it becomes apparent that they cannot wean from ventilatory support because of a flaccid myopathic quadriparesis. Some patients have only mild weakness, but many are severely affected. Conduction velocities and repetitive stimulation are normal. EMG reveals scattered spontaneous activity with small short-duration motor unit potentials that recruit in a myopathic manner; in severe cases the muscle may be electrically inexcitable. CK levels are elevated and muscle biopsy confirms some necrosis with loss of thick myosin filament and atrophy.

Acute severe necrotizing myopathy

Acute severe necrotizing myopathy is a rare condition that may develop after exposure to NMBAs with or without steroid therapy. Vecuronium seems to be more frequently associated with severe rhabdomyolysis.

Patients on steroids alone may develop acute steroid myopathy. This is a slowly evolving mild to moderate proximal weakness associated with mild elevation of CK and type 2 fibre atrophy. Because there are structural similarities between glucocorticoids and some non-depolarizing muscle blocking agents, a similar basis may underlie all of these conditions. Occasionally, direct sepsis may affect the muscle causing pyomyositis from septic micrometastases.

Neuromuscular disorders are important causes of failure to wean and prolonged morbidity in ICU. The disorders may have been present in patients before admission to the unit or develop as a secondary complication of their stay. Careful review of recent medical history, neurological examination and electrodiagnostic studies usually allow a definite diagnosis to be made. Prolonged neuromuscular blockade, AQM and CIP account for much of this weakness, but other relatively common disorders, such as Guillain–Barré syndrome or myasthenia gravis, should be considered. Occasionally, previously undiagnosed muscle disease can become evident when a patient is on an ICU for other reasons. Any muscle disease that can produce respiratory muscle weakness can lead to failure to wean, myotonic dystrophy being the most common (see non-invasive ventilation). Specific treatments may be available, but supportive care is the mainstay of treatment of most of these disorders.

Sleep and it's disorders

Structure of normal sleep

Sleep is a highly organized and regular process which is divided into stages defined by changes in EEG, electro-oculogram (EOG) and muscle tone (EMG). Four principle states of consciousness – wakefulness, light sleep, slow wave sleep (SWS) and rapid eye movement (REM) sleep – can be distinguished (Figure 19.16). As a subject falls asleep there is descent through four stages of deepening sleep during the first hour which is accompanied by a gradual slowing of the EEG rhythms. This is followed by ascent through the same stages culminating in REM sleep. The process is then repeated several times during the night. As the night proceeds the duration of the REM sleep stages increases, and deep sleep becomes less prevalent.

The onset of sleep is characterized by a brief transitional phase (stage 1) in which the alert and wakeful alpha rhythm (8–13 Hz) begins to slow, and slow theta (4–7 Hz) waves appear. EOG usually demonstrates rolling eye movements. Stage 2 sleep is characterized by the appearance on the EEG of episodic bursts of central, 14–16 Hz rhythms (sleep spindles) and 0.5–1 second high-amplitude central sharp waves (K complexes). In stages 3 and 4 sleep (SWS) the EEG is dominated by high-amplitude delta activity (<4 Hz). SWS is associated with slowing of cardiac and respiratory rate, lowered blood pressure, marked muscular relaxation and a reduction in metabolic rate by approximately 70% of normal levels. Normal values for sleep parameters in an adult are summarized in Table 19.22.

REM sleep

REM sleep is characterized by desynchronization of the EEG with the appearance of faster frequency rhythms. There are bursts of saccadic eye movements and profound relaxation of muscle tone in most major muscle groups of the limbs, neck and trunk including the diaphragm. Functional imaging during REM sleep shows that limbic regions, associated with emotional behavioural and experience, are activated during REM sleep, while regions of the frontal cortex are less active. Descending neuromuscular inhibition leads to profound muscular relaxation (atonia) of REM sleep. This may be important in preventing dream enactment.

The cyclic alteration in REM and non-REM sleep continues throughout the night. The first episode of REM generally occurs as the sleep stages ascend through light sleep after about 60–90 minutes following sleep onset and it is often relatively short. As rhythmic cycling continues, the length of time spent in REM tends to increase throughout the night while the time spent in SWS progressively decreases.

Regulation of wakefulness and sleep

The regulation of wakefulness and sleep depends on complex neuronal and biochemical interactions involving the cortex (basal forebrain), diencephalon (thalamus and hypothalamus) and brainstem. A number of neurochemicals are involved in the regulation of sleep including those that are: wake promoting (e.g. noradrenaline, acetylcholine, histamine, and dopamine); sleep promoting (e.g. melatonin and GABA) and both sleep and wake promoting (e.g. serotonin). More recently, the hypocretin (orexin) system has been shown to have a critical role in sleep regulation. The occurrence of REM sleep depends on the interaction between REM-inhibiting nuclei (raphe nucleus secreting serotonin, locus caeruleus secreting noradrenaline) and REM-promoting nuclei (laterodorsal and pedunculo-pontine tegmental nuclei secreting acetylcholine).

Regulation of the timing of the sleep cycles involves two mechanisms:

1 Central rhythm generation which is determined by a circadian oscillator located in the suprachiasmatic nucleus of the hypothalamus. This is influenced by light detected in the retina and melatonin. The oscillations are mediated by the cyclical transcription and translation of specific genes. The circadian rhythm affects not only sleep, but also other functions via the diurnal secretion of hormones from the pituitary and pineal gland.

2 Independent homeostatic mechanisms which are controlled by the time spent awake. It is suggested that the 'sleep debt' which builds up during long periods of wakefulness depends on the accumulation of 'somnogens', possibly adenosine, in the brain.

Functions of sleep

The functions of sleep remain unclear. The traditional role of sleep has been thought to be restorative but there is evidence to suggest a more complex mechanism in information processing such as memory consolidation. Even minor degrees of sleep deprivation have significant effects on cognition, memory and behaviour.

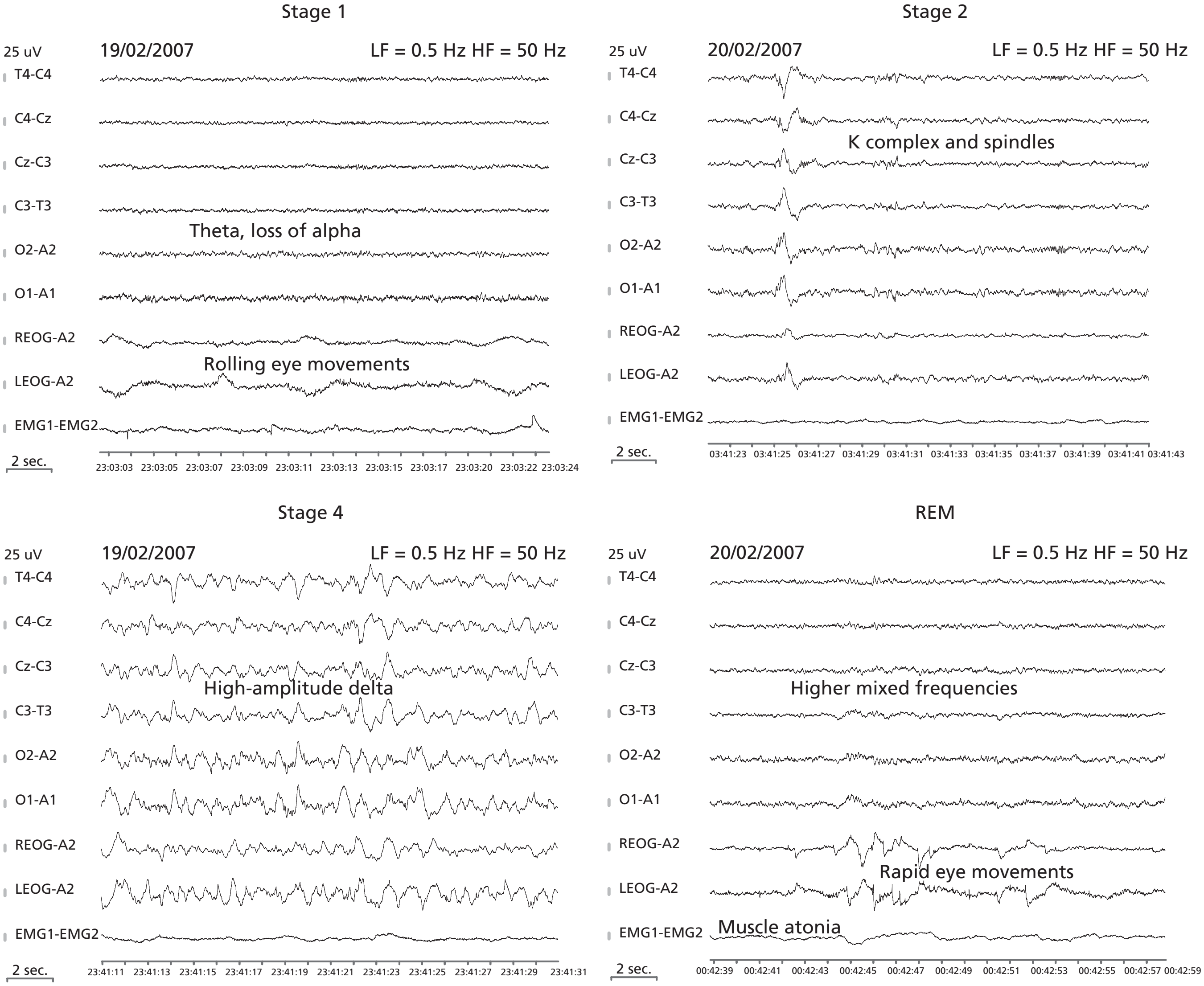

Stage 1
25 uV
19/02/2007
LF = 0.5 Hz HF = 50 Hz
T4-C4
C4-Cz
Cz-C3
C3-T3
Theta, loss of alpha
O2-A2
O1-A1
REOG-A2
Rolling eye movements
LEOG-A2
EMG1-EMG2
2 sec.
23:03:03 23:03:05 23:03:07 23:03:09 23:03:11 23:03:13 23:03:15 23:03:17 23:03:20 23:03:22 23:03:24
Stage 2
25 uV
20/02/2007
LF = 0.5 Hz HF = 50 Hz
T4-C4
C4-Cz
K complex and spindles
Cz-C3
C3-T3
O2-A2
O1-A1
REOG-A2
LEOG-A2
EMG1-EMG2
2 sec.
03:41:23 03:41:25 03:41:27 03:41:29 03:41:31 03:41:33 03:41:35 03:41:37 03:41:39 03:41:41 03:41:43
Stage 4
25 uV
19/02/2007
LF = 0.5 Hz HF = 50 Hz
T4-C4
C4-Cz
Cz-C3
High-amplitude delta
C3-T3
O2-A2
O1-A1
REOG-A2
LEOG-A2
EMG1-EMG2
2 sec.
23:41:11 23:41:13 23:41:15 23:41:17 23:41:19 23:41:21 23:41:23 23:41:25 23:41:27 23:41:29 23:41:31
REM
25 uV
20/02/2007
LF = 0.5 Hz HF = 50 Hz
T4-C4
C4-Cz
Cz-C3
Higher mixed frequencies
C3-T3
O2-A2
O1-A1
REOG-A2
Rapid eye movements
LEOG-A2
Muscle atonia
EMG1-EMG2
2 sec.
00:42:39 00:42:41 00:42:43 00:42:45 00:42:47 00:42:49 00:42:51 00:42:53 00:42:55 00:42:57 00:42:59

Figure 19.16 EEG recordings showing sleep stages.

Table 19.22 Approximate normal values for sleep parameters in an adult.

Sleep efficiency	>90%
Stage 1	10%
Stage 2	50%
Stage 3/4	20%
REM sleep	20%
Sleep onset	>10 minutes
REM sleep onset	90 minutes

Sleep and breathing

SWS sleep leads to an increase in parasympathetic tone and decrease in sympathetic tone leading to a reduction in heart rate, blood pressure and respiratory rate. REM sleep is associated with autonomic instability causing fluctuations in heart rate and blood pressure. The muscles of the upper airway relax during all stages of sleep (especially so in REM sleep) causing snoring and predisposing to the significant airway obstruction which underlies sleep apnoea or hypopnoea syndrome. Respiratory failure resulting from neuromuscular weakness is exacerbated during REM sleep because of the muscular relaxation involving upper airway, intercostal muscles and the diaphragm.

Classification of sleep disorders

Dyssomnias

The dyssomnias are sleep disorders associated with either a disturbed night's sleep or impairments of wakefulness, and produce

Table 19.23 Dysomnias.

Intrinsic sleep disorders
Idiopathic insomnia
Narcolepsy
Hypersomnia
Primary (idiopathic)
Recurrent:
Klein–Levin
recurrent stupor
Others:
post-traumatic
encephalitis lethargica
Obstructive sleep apnoea/hypopnoea syndrome
Periodic limb movement disorder
Restless legs syndrome
Extrinsic sleep disorders
Secondary insomnia
Insufficient sleep syndrome
Inadequate sleep syndrome
Environment, altitude
Drugs – hypnotics, stimulants
Alcohol, toxins
Circadian
Shift work sleep disorder
Jet lag syndrome
Delayed sleep-phase syndrome

insomnia or excessive daytime sleepiness or both. The dysomnias are divided into intrinsic, extrinsic (there is a secondary cause for the sleep disorder) and circadian (Table 19.23).

Insomnia

Insomnia is the complaint of 'poor sleep'; the duration or subjective quality of sleep is inadequate and non-restorative. Insomnia is extremely common and is said to merit treatment in 8–14% of the normal population. It is often associated with daytime fatigue but rarely daytime sleepiness. Although insomnia can be idiopathic, in many instances there is an underlying cause.

Several factors may contribute to insomnia: psychological difficulties, a variety of prescribed medications (particularly β-blockers) and non-prescribed drugs including caffeine, alcohol and substances of abuse, particularly cocaine and amphetamine. Sleep is also disrupted by depression, anxiety, stress, pain, cognitive impairment, pregnancy, nocturia and other medical disorders (especially respiratory and cardiac disorders). Insomnia may occur as a consequence of parasomnias (e.g. restless legs syndrome) causing interrupted sleep architecture. Neurological conditions that cause insomnia include those in which sleep is disrupted because of pain or discomfort (e.g. MS); those in which there is interference with sleep onset or maintenance; and those in which a structural lesion may interfere with sleep generation. In addition to the economic and social effects, chronic unremitting insomnia predisposes to psychiatric disorders including depression, anxiety and substance abuse.

Insomnia can result from prion disease. Fatal familial insomnia is a very rare hereditary prion disease caused by a mutation in codon 178 of the prion protein gene. It is characterized by insomnia, oneiric episodes (daytime dream episodes and enactment) and progressive neurological decline.

Management

In addition to addressing possible underlying causes, the first line is to teach, establish and maintain good sleep hygiene with a regular routine bedtime, the avoidance of nocturnal stimulants, stressful activity or exercise close to bedtime and daytime napping and establishing comfortable and regular sleep arrangements. Regular exercise not close to bedtime can increase and consolidate deep sleep. Cognitive–behaviour therapy can be a valuable technique in the management of chronic insomnia. Most drugs used in insomnia act as agonists at the benzodiazepine site of the gamma-aminobutyric acid A receptor ($GABA_A$); these drugs have effects other than their sedating action, including muscle relaxation, antiepileptic effects, anxiolytic effects, memory impairment, behavioural disturbance (especially in children) and ataxia. Some drugs have a more specific action (e.g. zolpidem, zaleplon and zopiclone) by targeting only specific $GABA_A$ subtypes. Drugs with longer duration of action may affect psychomotor performance, memory and concentration, and also have prolonged anxiolytic and muscle relaxing effects. Alternatively, benzodiazepines with too short a half-life may result in rebound insomnia and daytime hyperexcitability. Hypnotic drugs such as zolpidem and specific benzodiazepines are indicated for the management of acute insomnia or in the short-term management of chronic insomnia. There is a growing use of sedative antidepressants for longer term treatment of insomnia.

Primary (idiopathic) hypersomnia

Primary (idiopathic) hypersomnia is a rare disorder characterized by excessive daytime somnolence (EDS) but without cataplexy or nocturnal sleep disruption which usually starts in adolescence. The aetiology is unknown but there is a rare familial incidence. EDS is unaffected by prolonged sleep or frequent naps. Polysomnography (PSG) shows shortened sleep latency, increased total sleep time and reduced sleep latency and an absence of sleep onset REM periods. Primary hypersomnia is associated with low or normal levels of CSF orexin. However, it must be distinguished from narcolepsy without cataplexy or other causes of EDS. Recurrent hypersomnia may also occur in the Klein–Levin syndrome. This condition occurs in adolescence and is associated with a fluctuating course of hyperphagia, aggression and hypersexuality; prognosis is guarded as it does not respond well to treatment with stimulants, carbamazepine or lithium.

Idiopathic recurring stupor

Idiopathic recurring stupor is a rare syndrome occurring in males over 30 years and characterized by episodes of stupor and coma lasting hours to days with no obvious precipitating factors. The EEG demonstrates beta rhythms and the condition responds to the benzodiazepine antagonist flumazenil, raising the possibility that this condition results from endogenous benzodiazepine agonists.

Excessive daytime somnolence

EDS may also occur as a consequence of structural brain lesions, following head injury or encephalitis (particularly encephalitis lethargica) and are a complication of neurodegenerative conditions (e.g. Alzheimer's disease and idiopathic Parkinson's disease) and also in MS and myotonic dystrophy.

Narcolepsy

Narcolepsy is a primary disorder of alertness with an estimated prevalence of 3–5/10,000. It may develop at any age but the peak onset is between 15 and 30 years with a secondary peak in the fourth decade. Narcolepsy is rarely familial. However, the lifetime risk for developing narcolepsy is increased in first degree relatives of narcoleptic patients to 1%. The presenting symptoms are usually EDS, with irresistible sleep attacks during the day often occurring at inappropriate times. Other symptoms of this syndrome are cataplexy, sleep paralysis, hypnogogic hallucinations or vivid dream-like images, which characteristically occur at sleep onset and short periods of automatic behaviour also occur (micro-sleeps).

There may be a range of secondary symptoms related to sleepiness including visual blurring, diplopia and difficulties with memory and concentration. In combination, the symptoms of narcolepsy often have a major impact on relationships, education, employment, driving, mood and quality of life.

Cataplexy

Cataplexy is the occurrence of brief episodes of muscle weakness or paralysis precipitated by strong emotion, such as laughter, anger or surprise. There is a partial or complete loss of bilateral muscle tone. In its less severe form, cataplexy leads to transient bilateral ptosis, head droop, slurred speech or dropping things from the hands. Cataplexy may be severe enough to lead to complete collapse. The episodes are brief, lasting for seconds or minutes, but they may be followed by a sleep episode or occur recurrently (especially following sudden medication withdrawal) leading to status cataplecticus. Cataplexy is present in over 70% of people who have narcolepsy and can predate or follow the onset of other symptoms.

Hyponogogic/hypnopompic hallucinations

These are brief vivid dream-like episodes that occur at sleep onset or immediately before waking, and are often frightening or disturbing in nature. They are characterized by brief visual, tactile or auditory events, which continue for several minutes. They can occur during daytime naps.

Sleep paralysis and automatic behaviours

Sleep paralysis is the inability to move on waking from sleep. The episode can last from a few seconds to minutes but diaphragm and respiratory muscle activity continues. It is caused by the persistence of REM-related atonia on waking. Sleep paralysis is often associated with a hypnic hallucination often of someone pressing down on the chest or choking the person.

Short periods of automatic behaviour occur on wakening, characterized by absent-minded behaviour, nonsense speech or writing nonsense, reflecting the intrusion of sleep into the awake state. Nocturnal sleep disruption is also common, resulting paradoxically in insomnia.

Pathophysiology of narcolepsy

Narcolepsy is associated with abnormalities of the hypocretin–orexin neurotransmitter system. Low or undetectable levels of CSF hypocretin are found in most patients although some may have normal or raised levels. This has led to one hypothesis that in most patients there is a deficiency of hypocretin resulting from hypocretin neuronal loss in the hypothalamus. There may also be a form with 'hypocretin resistance' caused by abnormal hypocretin receptor–post-receptor dynamics leading to overproduction of hypocretin. Narcolepsy can also rarely occur secondary to tumours, encephalitis, head injury and MS. Narcolepsy-type symptoms can develop with inherited conditions such as Niemann–Pick type C disease, Norrie disease, Möbius syndrome and Prader–Willi syndrome.

Investigations

Polysonography (PSG) is important in excluding other causes of EDS including obstructive sleep apnoea, period limb movement disorder and REM-related behaviour disorder; however, all are more common in people with narcolepsy. PSG may also demonstrate early onset sleep (>10 minutes) and early onset REM (>20 minutes). The Multiple Sleep Latency Test (MSLT) is used to confirm the diagnosis. In this test the patient is allowed to fall asleep 4–5 times at 2-hourly intervals throughout the day and the latency to onset of sleep and REM sleep is measured. In narcolepsy, about 70% of patients will have a mean sleep latency of <5 minutes and a latency to REM sleep of <15 minutes on at least two occasions. These criteria have a specificity of 97% and a positive predictive value of approximately 70%. The presence of EDS, cataplexy and a typical MSLT allows a definite diagnosis of narcolepsy. The presence of two of these features renders the diagnosis probable, and other factors (such as the presence of other symptoms) need to be taken into account. Narcolepsy without cataplexy remains a diagnostic challenge and diagnosis is critically dependent on the MSLT and/or PSG.

There is a strong correlation between narcolepsy (with cataplexy) and HLA DQE10602 but this subtype is common in the general population and therefore the positive predictive value is low. Measurement of CSF hypocretin levels may become a standard diagnostic tool in narcolepsy but at present remains a research technique.

Management of narcolepsy

General management

Narcolepsy is a life-long condition with potentially wide-ranging implications. It is essential that patients and their relatives should have access to relevant and accurate information. Narcolepsy is entirely compatible with success both at school and in the workplace, but appropriate supportive provision may be necessary and career choices should take account of the possible hazards caused by EDS and cataplexy. Regular nocturnal sleep habits and attention to sleep hygiene help to minimize EDS, and planned naps can be used to optimize daytime performance. People with narcolepsy are required to declare the diagnosis to the Driver and Vehicle Licensing Authority and are advised not to drive until satisfactory control of symptoms is achieved.

Sleepiness

EDS is reduced by amphetamine-like stimulants, usually dexamfetamine, which is licensed for this use, or methylphenidate and modafinil. The use of modafinil is supported by randomized controlled trials. Advantages of amphetamine-like drugs include long experience, low cost, a possible action against cataplexy and higher efficacy; modafinil has the advantage that tolerance does not develop (which can occur with amphetamines) and possibly a lower rate of side effects. Common side effects of amphetamine-like drugs include irritability and insomnia while modafinil may cause headache, nausea and rhinitis, and may interact with the oral contraceptive pill; a pill with higher dose ethinylestradiol (at least 50 μg) is required.

Cataplexy

Cataplexy can often resolve with an improvement in nocturnal sleep and daytime somnolence. In addition, cataplectic symptoms often improve with age. Specific treatments include the tricyclic antidepressants (clomipramine) and the serotonin uptake inhibitors (fluoxetine). Other antidepressants, such as venlafaxine, can also be useful. These drugs also treat other narcolepsy symptoms. More recently, sodium oxybate (the sodium salt of gamma-hydroxybutyrate) has shown to be effective in cataplexy and may also improve daytime somnolence.

Obstructive sleep apnoea/hypopnoea syndrome

Obstructive sleep apnoea/hypopnoea syndrome (OSAHS) is the most common medical cause of daytime hypersomnolence and is associated with significant morbidity including an increased incidence of hypertension, cerebrovascular disease and road traffic accidents. It is associated with nocturnal sleep disturbance, unrefreshing sleep, difficulty in concentration and nocturnal choking. Sleep apnoea refers to a cessation in airflow during sleep ≥10 seconds while hypopnoea is defined as >50% reduction in airflow associated with oxygen desaturation >3% or arousal on EEG. OSAHS is considered moderate if there are more than 15 apnoeas/hypopnoeas per hour.

Obstruction of the upper airway usually occurs between the caudal soft palate and epiglottis. It is worsened during sleep when reduced upper airway muscle tone leads to collapse of the upper airway and obstruction. This is exacerbated by obesity (body mass index >28 kg/m^2), a narrow palate, crowding of the oropharynx and jaw or facial structural anomalies. Patients have difficulty falling asleep, loud snoring, stridor, coughing spells during sleep and restless sleep with frequent wakenings. There may be snoring and irregular breathing patterns and prolonged apnoea. Severe obstructive sleep apnoea is associated with morning headache, impaired memory, anxiety and the development of Pickwickian features with cor pulmonale.

Management

The first line management is weight loss, establishing regular sleep patterns and avoidance of alcohol, nicotine, caffeine and sedatives in the evening. Investigation and appropriate treatment of co-morbidity, particularly hypothyroidism, is mandatory. CPAP by nasal or face mask is effective in OSAHS, improving sleep architecture, nocturnal oxygenation and the symptoms of sleepiness, impaired cognition, mood and driving ability and cardiovascular function. However, its use requires considerable educational support and technical back-up. Compliance may be variable in the less severe forms of the condition because of poor mask fitting, dryness of the mouth and airways, claustrophobia, aerophagia and social difficulties. Oral appliances such as mandibular repositioning splints may be valuable in improving EDS and the cardiovascular complications of mild OSAHS. They work by holding the mandible forward, thus increasing the upper airway space by advancing the tongue and possibly changing genioglossus activity. Surgical treatment (uvulopalato-pharyngoplasty) does not have a role. Tracheostomy may be necessary in patients with incipient cor pulmonale.

Restless legs syndrome

Restless legs syndrome (RLS) affects 2–5% of the population but is more frequent in the older age group. It is characterized by uncomfortable dysaesthesiae, in the calves and feet leading to an urge to move the limbs and motor restlessness which, transiently, relieves the symptoms. The discomfort is worse at rest, especially in the evening or at night, and may lead to difficulty getting to sleep, frequent awakenings, reduced sleep efficiency and severe insomnia. Leg jerking may also occur during wakefulness and be independent of the dysaesthesiae. RLS usually follows a chronic and often progressive course with intermittent fluctuations, but there may be prolonged periods of remission. Periodic limb movements of sleep are commonly associated with RLS. The condition is usually isolated but may occur in association with pregnancy, iron deficiency anaemia, chronic renal failure, small fibre neuropathies, polymyalgia rheumatica, intermittent claudication and nocturnal leg cramps; there is a significant familial incidence.

RLS may be difficult to relieve completely. Any underlying cause should be sought and treated and there should be careful explanation and attention to any psychological or social factors that may be exacerbating the situation. Levodopa preparations lead to substantial relief in >50% and short-term benefits in 85% with improved sleep efficiency and less arousals or periodic limb movements; however, the benefits are often poorly sustained and repeated dosage adjustment and medication changes are often necessary. Bromocriptine, pergolide and ropinirole are also effective in controlled trials. Symptomatic relief can also be achieved with benzodiazepines, gabapentin and opioids.

Periodic limb movement disorder

Periodic limb movement disorder (PLMD) is extremely common, with more than 30% of individuals over 65 years having a significant number of periodic limb movements. They are characterized by jerking and kicking of the limbs occurring with varying frequency and localization during sleep. They occur in bouts of dozens or more lasting for many minutes and recurring every 20–30 minutes. Although PLMD may be asymptomatic, patients may have complaints of difficulty falling asleep, frequent awakenings, daytime sleepiness or because bed partners may actually complain more about movements. The sensory symptoms and waking dyskinesiae characteristic of RLS do not occur. They can be associated with other sleep disorders including RLS, sleep apnoea, narcolepsy or REM behaviour disorders or, most commonly, as an isolated phenomenon. The movements are most frequent during stage 1 and 2 sleep, less frequent during SWS and generally absent during REM sleep except in associated with narcolepsy or sleep apnoea. Treatment is only justified if periodic limb movements are symptomatic and follows the same principles as RLS.

Circadian rhythm disorders

Intrinsic circadian rhythms maintain a sleep–wake cycle of approximately 24 hours. They are set by environmental day length and are influenced by social activity, which can adjust timings. A mismatch between the internal circadian cycle and the external environment leads to insomnia, EDS and disruptive sleep function and activities of daily living. These may occur because of alterations in the internal circadian cycle (i.e. delayed or advanced sleep phase syndrome) or to changes in the environment (e.g. jet lag).

Delayed or advanced sleep phase syndrome

These conditions are characterized by an inability to fall asleep or remain asleep at a conventional time. The persistence of the pattern distinguishes the condition from alterations in sleep rhythms, change in work timetables or travel across time zones. These conditions may be difficult to manage as attempts to regularize rhythms can lead to prolonged sleep latency and chronic insomnia, resulting in the excessive use of stimulants, hypnotics or alcohol. These conditions can be helped by cognitive–behavioural therapy, and a regimen of planned advancement of bedtime. Bright light therapy and melatonin may also be of some benefit.

Shift work and jet lag

These conditions occur when the physical environment is altered and there is a mismatch with the internal circadian cycle. Many social factors influence the ability to acclimatize to a change in routine or travel including age, community, work responsibility and stress. They may lead to EDS or insomnia and a deterioration in the performance at work and a dependence on medication. Melatonin has been shown to have a benefit in these conditions.

Parasomnias

Parasomnias are undesirable motor, verbal or experiential phenomena that occur during the sleep period and may be considered disorders of sleep state transition, partial arousal or arousal. They are categorized as primary (disorders of sleep state) and secondary (disorders of other organ systems manifest themselves during sleep). The primary sleep parasomnias can be classified according to sleep state of origin (Table 19.24).

Table 19.24 A classification of parasomnias.

Primary parasomnias
Normal sleep–wake transition phenomena
Sleep starts
Hypnic jerks
Motor, visual, auditory & somatosensory phenomena
Hypnagogic imagery

Arousal disorders (typically arising in NREM sleep)
Sleep walking
Sleep terrors
Confusional arousals

REM-related
REM-related behaviour disorder (RBD)
Nightmares
Sleep paralysis

Others
Rhythmic movement disorders
Fragmentary myoclonus
Bruxism
Enuresis
Nocturnal paroxysmal dystonia
Snoring
Sleep talking

Secondary parasomnias
Headaches – vascular, exploding head, hypnic headache
Cardiorespiratory, e.g. cardiac failure, angina, respiratory dyskinesias
Gastrointestinal, e.g. gastro-oesophageal reflux
Functional disorders

Non-REM parasomnias

Sleep–wake transition disorders are non-REM phenomena that occur in the transition between waking and sleeping. Hypnic jerks (sleep starts), sleep talking and nocturnal leg cramps all commonly occur in otherwise healthy individuals and are regarded as physiological alterations rather than pathological conditions. Hypnic jerks are brief body jerks at sleep onset, which may involve limbs, trunk or head. The jerks may be single or repetitive and may be spontaneous or provoked by stimuli. Visual, auditory or somatosensory sleep starts may also occur. In non-REM sleep, small flickering movements called sleep myoclonus are associated with very brief, highly localized EMG potentials. In some cases, the amplitude and frequency of these movements increase, at which points they are called fragmentary myoclonus.

The exploding head syndrome is also a form of parasomnia and may represent a form of sleep start in which there is a sudden arousal during transition into sleep with a sensation of a loud noise 'bursting' the head. They can also occur during REM. Hypnic headache is rare, occurring in older patients, regularly at constant times at night. The headache is diffuse, protracted and relatively mild.

The arousal disorders are also abnormal non-REM sleep phenomena and consist of confusional arousal, sleep walking and sleep terrors. The conditions are characterized by a family history, a tendency for the disorder to arise from slow wave sleep (stage 3 and 4) and a higher incidence in childhood. They represent incomplete awakenings from sleep, most commonly deep slow wave sleep.

Sleep walking is common in children, but also occurs in adults. It arises from a deep sleep, typically in the first third of the night, and may be either calm or agitated, with varying degrees of complexity and duration. Repetitive behaviours may occur and occasionally eating may be a feature. The episodes usually last 1–2 minutes but prolonged complex behaviours including driving have been reported. It is often very difficult to awaken the patient who is then confused with variable amnesia for the event. The most important consideration is protection from injury. Treatment is often unnecessary but precipitating factors such as sleep deprivation and alcohol should be avoided; drug treatment with benzodiazepines or tricyclic medication may be valuable.

Sleep terrors are the most disturbing disorder of arousal for the patient and family. They are often characterized by a loud scream associated with extreme panic and prominent, occasionally violent, motor activity, resulting in bodily injury or property damage. The patient is inconsolable during the terror and amnesic for the event, which may be complete. Often, people report dream-like episodes in which they are being attacked or chased. The patient appears to be in a state of acute terror with tachycardia, tachypnoea, mydriasis and increased muscle tone. They last between 30 seconds and 3 minutes and can occur from early childhood. Treatment is rarely necessary but diazepam and tricyclic medication are helpful. Sleep terrors characteristically begin during the deep sleep of the first third of the night; however, when episodes are very frequent they may be diffusely distributed across the sleep period and occur in any non-REM stage. Sleep terrors are sometimes familial and are associated with increased incidence of sleep walking and confusional arousals.

Confusional arousals usually occur in children and are characterized by partial awakening movements in bed, occasional thrashing about or inconsolable crying and associated with confusion and impaired mentation, disorientation in time and place, and perceptual impairment. Behaviour is often inappropriate and aggressive behaviour may be observed, indeed murder has been committed immediately on sudden arousals from deep sleep. Confusional episodes are usually brief but may last up to 30 minutes. Confusional arousals can be associated with disorders causing deep or disturbed sleep, including metabolic, toxic and other encephalopathies; idiopathic hypersomnia; symptomatic hypersomnia and sleep apnoea syndrome.

Episodic nocturnal wanderings are nocturnal episodes in adults, characterized by abrupt arousal followed by motor activities such as kicking, leaping, head banging and violent ambulation associated with screaming, yelling and unintelligible speech. The patient seems afraid, completely unresponsive to the environment and at risk of injury. The attacks usually occur in clusters during non-REM sleep stage 2 and all respond well to carbamazepine.

Disorders of arousal may be triggered by pyrexia, alcohol, prior sleep deprivation, emotional stress or a variety of medications including sedatives and hypnotics, neuroleptics, minor tranquillizers, stimulants and antihistamines. They are also exacerbated by pregnancy and menstruation. Treatment is usually unnecessary with adequate reassurance. However, tricyclic antidepressants and benzodiazepines may be effective if the behaviours are dangerous to persons or property or are disruptive to the family. Cognitive behavioural therapy may be particularly helpful.

Bruxism is intermittent repeated grinding or clenching teeth during sleep which is common in children and also in the severely disabled and may appear to any sleep stage. It may be associated with other movement disorders during sleep. Sleep bruxism may be a manifestation of mild REM sleep behaviour disorder. There is no satisfactory treatment although attempts are made at occlusal adjustment and splints.

REM sleep disorders

REM-related parasomnias with movement disorders include nightmares, sleep paralysis and REM sleep behaviour disorder. Nightmares are dreams with progressive content that become frightening. They usually last only a few minutes and are associated with movements, mumbling and vocalization before awakening. They occur in the second half of the night during REM sleep and may be related to REM rebound during a period of recuperation after REM sleep deprivation from either stress, drugs or surgery. Terrifying hypnagogic hallucinations (sleep onset nightmares) are part of the narcoleptic tetrad but may also occur in isolation. They are nightmares occurring at sleep onset in association with sleep onset REM. The usual treatment is tricyclic antidepressants especially clomipramine which appears effective both for episodes in non-REM and in REM sleep onsets.

REM sleep behaviour disorder (RBD) is a rare condition that occurs predominantly in older men. It is characterized by 'dream enactment' causing abnormal behaviour during REM sleep, including generalized limb or truncal jerking which may progress to prominent, violent or more complex disruptive sleep behaviours, which are often aggressive, confrontational and may be violent with patients enacting intense dreams occasionally leading to self-injury. The duration is 2–10 minutes, recurring a few times a week. Twenty-five per cent have a prodrome involving subclinical behavioural release during sleep characterized by talking, yelling or vigorous sleep-related movements which precede the full-blown episode by a number of years. REM sleep disorder is characterized by loss of intermittent REM sleep atonia, and by the appearance of elaborate motor activity associated with dreams. The condition may be idiopathic or associated with neurodegenerative disorders (parkinsonism, multi-system atrophy, Lewy body dementia), narcolepsy, cerebrovascular disease, MS or Guillain–Barré syndrome. RBD may develop months or years before the onset of any underlying neurological disorder. RBD may also emerge during withdrawal from ethanol or sedative-hypnotic abuse and with anticholinergic and other drug intoxication states leading to loss of REM atonia. Clonazepam is an effective treatment in RBD in suppressing both the violent behaviour and the intense subjective dream recall by suppression of phasic EMG activity during REM sleep rather than by restoration of REM atonia. Adjunctive or alternative medication may involve imipramine, carbamazepine, levodopa or gabapentin. It may be necessary for the patient or partner to take self-protective measures.

Other forms of parasomnia

Rhythmic movement disorders

Rhythmic movement disorders (*jactatio capitis nocturna*) are a group of behaviours characterized by stereotyped movements (rhythmic oscillation of the head or limbs, head banging or body rocking) which typically occur just before sleep onset and persist into light sleep. They most commonly occur in infants and young children often associated with autism and mental retardation, but have been described in adults with normal IQ. Significant complications include scalp and body wounds, subdural haematoma, retinal petechiae, skull callus formation and significant family and psychosocial problems. There are no EEG signs of arousal during the rocking movements.

Nocturnal paroxysmal dystonia

Nocturnal paroxysmal dystonia (NPD) are sleep-related attacks in which intense stereotypical choreoathetotic, dystonic and ballismic movements occur and can cause severe sleep disruption with EDS or injury to the sleeping partner. Two varieties exist: a short-lived form lasting 15–60 seconds (resembling paroxysmal kinesogenic dystonia of wakefulness) and a prolonged form that lasts up to an hour. The nature of the movements is similar in both varieties. The attacks arise from light sleep with the eyes remaining open and may recur several times a night for many years. The nature of NPD remains uncertain but the present evidence indicates that NPD with short-lasting attacks represents a peculiar nocturnal epileptic seizure, probably of frontal lobe origin, characterized by their occurrence during non-REM sleep, negative EEG and good response to carbamazepine.

Other sleep disturbances in extrapyramidal disease

In extrapyramidal disorders, particularly idiopathic Parkinson's disease (PD), Huntington's, Tourette's syndrome and torsion dystonia, involuntary movements may persist during sleep. These usually occur during stage 1, 2 and REM sleep and are less common in stage 3 and 4 sleep. Sleep difficulties are particularly frequent in patients with PD and these include difficulty getting to sleep, inadequate time asleep, disrupted sleep and daytime sleepiness which may occur as a result of nocturia, inability to turn over during the nights or on waking, inability to get out of bed unaided, leg cramps and jerks, dystonic spasms of the limbs or face and back pain during the night. There may be an increased prevalence of PLMD, RLS and RBD in association with PD.

The treatment of PD itself may alleviate abnormal motor activity during sleep but separate treatment may be necessary and clonazepam is particularly valuable. Respiratory disturbances, characterized by involuntary movements of laryngeal or respiratory muscles and impaired volitional control, are common in PD, progressive supranuclear palsy (PSP) and multiple-system atrophy. There are also sleep-fragmenting respiratory disorders, such as sleep apnoea or upper airway resistance syndrome, a restrictive type of lung defect caused by an intrinsic defect in breathing control, impaired respiratory muscle function caused by rigidity and faulty autonomic control of the lungs. PD patients may also have obstructive respiratory defect, stridor or laryngeal spasm associated with off states or dystonic episodes, diaphragmatic dyskinesiae, drug-induced respiratory arrhythmias and dyspnoea and upper airway dysfunction with tremor-like oscillations.

Dystonic movements and tics may persist during sleep at a reduced frequency and amplitude but are maximally active during stage 1 and 2 and REM sleep episodes.

Epilepsy syndromes associated with sleep

It is essential to distinguish the sleep-related paroxysmal events described above from nocturnal epilepsy and it may be difficult on history alone to distinguish epilepsy from cataplexy, confusional arousals, night terrors and RBD. Epilepsy has a complex association with sleep. Certain seizures are more common during sleep such as frontal lobe seizures that occur during non-REM sleep. Rarely, nocturnal seizures may be the only manifestation of an epileptic disorder and these can be confused with a parasomnia – this has been especially true for autosomal dominant nocturnal frontal lobe epilepsy, the seizures of which were thought originally to represent an NPD. Nocturnal frontal lobe seizures are brief, stereotypical, cluster and occur at any time of night.

Many cases of episodic nocturnal wanderings are possibly seizures or post-ictal confusion. Rarely, non-convulsive status epilepticus can occur during slow wave sleep; the clinical manifestation of this is usually intellectual regression and autism. Lack of sleep can precipitate seizures especially in the idiopathic generalized epilepsies, and sleep apnoea has been reported to worsen seizure control. Sleep disturbances also commonly occur in people with epilepsy in whom there is a higher incidence of sleep apnoea, fragmented sleep and insomnia as well as daytime somnolence (often drug-related).

Acknowledgement

The authors are grateful to BMJ Publications for permission to reproduce sections from Howard R. *et al*. Admission to neurological intensive care: who, when and why? *J Neurol Neurosurg Psychiatry* 2003; **74**: 2–16.

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20

Neuro-Oncology

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Neuro-oncology covers the scientific and clinical basis of CNS tumours and neurological complications of cancer. In common with many other areas of medicine, a multi-disciplinary approach provides optimal standards of care. The emergence of new therapies throughout neurology has changed the role of neurologists from diagnostic to therapeutic clinicians. This is especially relevant in neuro-oncology. Improvements in diagnosis and surgical technique, new biological agents and increasing use of combined radiotherapy and chemotherapy for tumours such as gliomas have led to small but definite improvements in survival.

There is increasing awareness amongst neurological trainees of the large array of CNS tumour types, the spectrum of neurological complications of cancer, particularly paraneoplasia, and the neurotoxicity of chemotherapy and radiotherapy, making it essential to have up-to-date knowledge. This chapter provides a clinically dominated guide to the key issues in neuro-oncology. The initial sections reflect the highly specialized nature of disciplines within neuro-oncology. The multi-disciplinary aspects of care are outlined in the sections on clinical management.

Epidemiology of common primary intracranial tumours

Incidence

Brain tumours include primary tumours arising from intracranial structures and metastases from outside the CNS. Primary CNS tumours account for approximately 8% of all cancers in adults and 2% of all cancer deaths; broadly, there is a 25% chance of any adult patient who has a brain tumour dying from it. Some 20% of malignancies in childhood are within the CNS. In adults they are second only to stroke as a cause of neurological death. They place a considerable burden of suffering on patients, their families and carers.

Incidence figures for brain tumours depend much on methods of case ascertainment. Incidence of specific tumour types is believed to be much the same worldwide. The crude UK annual incidence for primary tumours is 15.3/100,000 and for secondary tumours 14.3/100,000 patients. It is likely that the true incidence is considerably higher. One study from the south-west of England ascertaining data mainly from radiology records found the crude annual incidence for primary tumours to be 21/100,000. There are some suggestions that the incidence of glioma and CNS lymphoma is increasing, particularly in elderly patients. This may simply be because of better case ascertainment and the increasing use of imaging, e.g. for patients presenting with stroke.

Different tumour types present in different age groups. Supratentorial gliomas are uncommon below the age of 30 years but become increasingly prevalent thereafter. They account for over 60% of primary tumours. The most frequent tumours of adolescence are germ cell tumours and astrocytomas, those in middle life astrocytomas, meningiomas and pituitary adenomas and in later life, highly malignant astrocytomas and metastases. Infratentorial tumours are more common in childhood. Seventy per cent of paediatric primary intracranial tumours arise in the cerebellum and brainstem, specifically astrocytomas, ependymomas and medulloblastomas. Meningiomas and schwannomas occur more frequently in women; the reverse is true for astrocytomas.

Survival

The survival of a patient with a brain tumour is related to age, performance status, histological type, grade and location. Intra-axial tumours are associated with poorer survival than extra-axial. Although there has been some improvement over the last 30 years, only about 30% of adults with malignant brain tumours in the UK survive 1 year and 15% survive 5 years. This compares

Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

to a 5-year survival rate of 17–20% in Europe and 25% in the USA. These discrepancies may be partly because of inclusion of benign brain tumours, certainly in US registries. As a general rule, young patients fare better than older with the same histological types. Patients with benign tumours, e.g. meningiomas, may survive many decades or be cured permanently. Children with brain tumours survive for longer than adults: 5-year survival in children is around 60%. Histological grading has particular prognostic implications and is an essential part of the neuropathological assessment. This is especially so because brain tumours rarely spread outside the nervous system. They are therefore not classified with the familiar TNM (tumour, node, metastasis) system. Prognosis is usually expressed in terms of percentage survival at 5 years. For astrocytomas, 5-year survival is over 85% for WHO Grade I tumours, around 50% for WHO Grade II tumours, 20% for WHO Grade III tumours and less than 5% for WHO Grade IV tumours.

Risk factors

The cause of most brain tumours remains unknown. The only definite environmental risk factor is ionizing radiation, either following nuclear explosions or therapeutic radiation. Cranial radiotherapy (RT) even at low doses has been shown to increase the relative risk of meningiomas by a factor of 10 and of gliomas by a factor of 3. Other RT-induced tumours include sarcomas and schwannomas. They have been described following RT for tinea capitis, craniopharyngioma, pituitary adenomas and prophylactic cranial irradiation for acute lymphoblastic leukaemia. Secondary tumours tend to lie within the radiation field, usually within lower dose regions, and develop from a few years to many decades after RT. The median time to the development of gliomas is 7 years. Sarcomas develop with a longer lag time and meningiomas may be seen 30–40 years later. The histology is identical to spontaneous tumours although meningiomas are more likely to have atypical histology.

No other environmental risk factor has been clearly identified. There has been widespread concern about cellular phones. Case–control studies have shown no increased risk of any brain tumour related to type of phone, duration and frequency of use and cumulative hours of use. However, with the exponential increase in the ownership and duration of use of cellular phones, particularly in children, it is vital that brain tumour trends continue to be surveyed to detect a latent interval, which might be several decades.

Genetic causes of brain tumours are rare but important. Occasionally, brain tumours occur in successive generations without any other tumour predisposition. Typically, they are associated with neurocutaneous syndromes such as neurofibromatosis (optic nerve glioma, meningioma, vestibular schwannoma), tuberous sclerosis (subependymal giant cell astrocytoma) and von Hippel–Lindau syndrome (haemangioblastoma). There are also rare familial tumour syndromes, e.g. Li–Fraumeni syndrome (glioma) and Cowden's disease (dysplastic cerebellar gangliocytoma or Lhermitte–Duclos disease).

Clinical features

The clinical presentation of a brain tumour depends on location, rate of growth and pathology. Any tumour has the potential to produce a focal deficit and raised intracranial pressure although this is most commonly seen with high-grade tumours because of rapid growth and brain tissue necrosis and with posterior fossa mass lesions. In contrast, low-grade tumours are infiltrative, less destructive than their high-grade counterparts and present more frequently with a seizure disorder.

Several hospital-based studies have examined the clinical features of brain tumours. One study of over 300 brain mass lesions showed that headache and seizures were the most frequent symptoms followed by neurological deficit and cognitive behavioural changes. Patients with cognitive decline tended to be diagnosed late and had developed focal or multiple symptoms by the time they were seen. Asymptomatic papilloedema and hemianopia was noted in particular, pointing to the need for careful fundoscopy and visual field testing.

Headache

Tumours can produce raised intracranial pressure either by the mass effect of a rapidly growing lesion with associated vasogenic oedema or by blockage of CSF pathways, typically seen with posterior fossa tumours and with intraventricular tumours. Stretching or distortion of the meninges can give rise to headache without raised pressure. Intra-tumoural haemorrhage can produce an acute rise in pressure leading to severe headache with coma or reduced consciousness. This clinical picture is also sometimes seen with large tumours without any evidence for a bleed, particularly in periventricular locations where encystment of a horn of the lateral ventricles can occur.

Severity of headache is not a helpful diagnostic pointer – indeed, the most severe headaches encountered in practice are almost invariably caused by primary headache syndromes such as migraine or cluster headache. One study of over 100 patients with brain tumours revealed that headaches were present in nearly half, equally for primary and metastatic tumours, and that they were similar to tension-type headaches or migraine in over 80%. The typical tumour headache was bi-frontal, worse on one side but it was the worst symptom in under half of the patients. Brain tumour headaches were worse with bending in around one-third, unlike true tension-type headaches. Nausea or vomiting was present in 40%. Early morning headache was uncommon. Nausea and vomiting, abnormal physical signs or a significant change in prior headache pattern were particular risk factors for a tumour.

What usually distinguishes headaches of a brain tumour from benign headaches is the gradual evolution of associated symptoms, i.e. focal deficit, seizures, ataxia and vomiting, the latter being seen particularly with posterior fossa tumours. It is quite exceptional for a patient with a brain tumour to present with headache alone.

Seizures

Tumour-associated seizures may be partial and/or generalized. There is an inverse relationship between tumour grade and occurrence of seizures and certain low-grade tumours, e.g. oligodendrogliomas and gangliogliomas are associated with seizures in over 90% of cases. The type of seizure is dependent on tumour location and there are no distinguishing features of focal seizures to distinguish a tumour from a non-neoplastic process. In a recent retrospective study of over 80 adults with supratentorial low-grade gliomas, seizures occurred in all but one and only 30% of patients became seizure-free on anticonvulsants. There was no clear association between severity of the seizure disorder and behaviour of the underlying tumour, in particular the return of seizures after a period of seizure freedom did not invariably indicate tumour recurrence.

Focal deficits

Focal deficits depend on the location of the tumour and are usually subacutely progressive. However, stroke-like presentations, and even TIAs, are well recognized. These are sometimes caused by intra-tumoural haemorrhage and sometimes by presumed vascular changes associated with the tumour. Progressive focal deficits occur typically in patients with high-grade tumours, e.g. glioblastoma multiforme and brain metastases, rather than with low-grade tumours, presumably because of the ability of the latter to infiltrate normal tissue without interfering with function.

Cognitive and behavioural symptoms

A minority of patients with tumours present with cognitive symptoms and/or a behavioural disorder, e.g. abulia caused by a subfrontal meningioma. Specific focal cognitive deficits e.g. alexia, acalculia may be seen in tumours affecting the dominant parietal lobe particularly around the angular gyrus. Psychiatric symptoms such as depression, paranoid delusions and personality changes are all well recognized and stress the need for imaging in patients with atypical affective disorders.

Endocrine symptoms

Pituitary and hypothalamic tumours may present with endocrine disturbances brought about by anterior or posterior pituitary failure or oversecretion, e.g. acromegaly. They may also cause visual failure typically commencing with bitemporal quadrantanopia or hemianopia as the optic chiasm is further compressed. Pituitary tumours are discussed below.

Unusual symptoms

Other presentations of tumours include:

- Anosmia: orbital plate tumours (Chapter 12);
- Cranial nerve lesions: skull base and cerebellopontine angle tumours;
- Cachexia: hypothalamic tumours; and
- Precocious or delayed puberty: craniopharyngiomas.

Pathology of common primary brain and spinal tumours

Histogenesis

The nomenclature of brain tumours has relied on the resemblance of tumour cell shape, morphology and localization to those of differentiated cells of the brain or expression of glial or neuronal proteins, identified by immunohistochemical techniques. Thus, gliomas are thought to arise from neoplastic transformation of astrocytes, oligodendrocytes or their precursors. Currently, it is impossible to demonstrate directly which cell of origin gives rise to which specific glioma in humans. This remains a fundamental question in glioma biology. Possibilities include differentiated astrocytes, oligodendrocytes, glial progenitor cells or even cells originating from the stem cell compartment of the adult brain. It may be that the initial genetic mutation determines the final tumour phenotype independent of the original cell type, in which case the identity of a differentiated cell may alter during the process of transformation, as more genetic mutations arise resulting in progressively more undifferentiated tumours.

There is increasing interest in the role of stem cells in the origins of brain tumours. These are defined as cells that have the ability to perpetuate themselves through self-renewal and to generate mature cells of a particular tissue through differentiation. There are numerous parallels between somatic stem cells and cancer cells. Both show self-renewal, differentiation and capacity for histogenesis. Somatic stem cells self-renew in a highly controlled manner and differentiate into mature cells which go on to form normal tissues, whereas cancer cells show poorly controlled self-renewal, often abortive differentiation and go on to form abnormal tissues. The observation that only a small minority of tumour cells show an indefinite potential for self-renewal *in vitro* or *in vivo* gave rise to the hypothesis that tumours are composed of both cancer stem cells and more differentiated cells. The existence of a cancer stem cell has been proven for acute myeloid leukaemia, breast cancer ($CD44^+/CD24^-$ cells), glioblastoma and medulloblastoma ($CD133^+$ cells). Implications of the cancer stem cell hypothesis are:

- Cancer cells can be hierarchically organized in that they range from poorly differentiated, highly proliferative cells to more mature, less proliferative forms;
- Cancer cells share cell cycle pathways that are relevant to normal human development and control of growth.

Molecular pathways involved in tumour formation

An intrinsic difficulty in the study of signalling pathways involved in oncogenesis is the abundance of mutations that accumulate during the multi-step process of malignant transformation of normal cells into tumour cells. An additional obstacle is the heterogeneity of mutations within a single tumour which suggests separate subpopulations of cells are capable of promoting growth in the same malignancy.

Three types of genes are involved in tumorigenesis:

1. Oncogenes;
2. Tumour suppressor genes; and
3. Repair/stability genes.

Oncogenes and tumour suppressor genes regulate cell division, control apoptosis or cell cycle arrest, while repair/stability genes become tumorigenic by loss of their DNA repair function. Oncogenes are genes that under normal conditions, i.e. development and cell self-renewal, promote cell birth and growth but when unleashed become autonomously active. For example, a point mutation in *c-kit*, which codes for a tyrosine kinase, leads to constitutive activation in the kinase domain and is causally implicated in the pathogenesis of gastrointestinal stroma tumours which arise from Cajal cells. In contrast, tumour suppressor genes are gatekeepers of cell cycle function and under physiological conditions exert a negative regulation on processes promoting the cell cycle. They may also control apoptosis and therefore mutations in these genes can lead to a failure of apoptosis. Typical examples are:

- *p53:* the 'guardian of the genome' which causes induction of apoptosis in response to cell damage;
- *Retinoblastoma (Rb):* the prototypic tumour suppressor gene which controls the cell cycle at G1; and
- *PTEN* (phosphatase and tensin homologue): mutations are associated with Cowden syndrome and other hamartomatous disorders.

All of these are abnormally expressed in gliomas.

Repair/stability genes normally function by repairing DNA damage–mismatch repair, nucleotide excision repair and base excision repair. Under normal conditions, DNA damage is kept to a minimum, but loss of function results in accumulation of DNA mutations and eventually tumour formation.

Mutations in oncogenes, tumour suppressors and repair/stability genes can occur in the germ line, resulting in hereditary tumour syndromes or in somatic cells, causing sporadic tumours. The initial event in the neoplastic process is a single somatic mutation resulting in a growth advantage of a clonally expanding cell population. Additional mutations then accrue and cause further series of clonal expansions, eventually resulting in a tumour.

The cell cycle is controlled by a cascade of genes, which may either promote or suppress it: for example, mutations of cdk4 and cyclin D1 in the Rb pathway are oncogenic, i.e. activating, while mutations of Rb and p16, both tumour suppressor genes, lead to inactivation. Hence, the combinations of these mutations result in activation of the same pathway. However, despite the detailed knowledge of pathway function, it still remains unclear what eventually determines the phenotype of a brain tumour – is it the initial mutation, the sequence of subsequent mutations or the differentiation state of the cell in which the initial genetic event occurs? As a corollary of this complexity and multiplicity of mutations in an advanced tumour, it is impossible to track back to the primary event. Hence, *in vivo* models are needed in which specific pathways in stem cells can be altered to study the genotype–phenotype correlation of brain tumours.

WHO classification of CNS tumours

Most brain tumour classifications are based on the work of Bailey and Cushing (1926) who named tumours after the cell type in the developing embryo, fetus or adult that most resembled the tumour histologically. The classification system most widely accepted is that of the World Health Organization (WHO 2007) which recognizes more than 120 different tumour types, and is shown in Table 20.1.

Neuroepithelial tumours

Neuroepithelial tumours form the vast majority of intrinsic brain tumours and encompass a broad spectrum of neoplasms that arise from or share morphological properties of neuro-epithelial cells. Accordingly, they are further subgrouped into:

- Glial neoplasms, which include astrocytic, oligodendroglial and ependymal tumours;
- Tumours with predominant neuronal phenotype, such as ganglioglioma, dysembryoplastic neuro-epithelial tumour and neurocytoma;
- Neuroblastic tumours;
- Pineal tumours;
- Embryonal tumours such as medulloblastoma; and
- Choroid plexus tumours.

The grading of gliomas and other tumours in the WHO scheme is based on the presence of certain morphological characteristics within the tumour: cellular and nuclear atypia, mitotic activity, vascular endothelial proliferation and necrosis. These features reflect the malignant potential of the tumour in terms of invasion and growth rate. Tumours without any of these features are WHO Grade I; those with atypia alone are WHO Grade II. Those tumours with atypia and mitosis are WHO Grade III and those with vascular proliferation or necrosis or both are WHO Grade IV. Grade I and II tumours are termed low grade and Grade III and IV tumours high grade. In one subset of astrocytomas the usual four-featured grading system is not used, because of their distinctive cell appearance. Tumours in this subset may have endothelial proliferation and marked atypia; nevertheless, they are slow growing, well circumscribed and thus low grade:

- Juvenile pilocytic astrocytoma;
- Pleomorphic xantho-astrocytoma; and
- Subependymal giant-cell astrocytoma.

Plates 20.1 and 20.2 illustrate the histological features of some common tumours.

Astrocytomas

Astrocytic tumours comprise a wide range of neoplasms differing in their location, age distribution, biology and clinical course. The most common are the astrocytomas, subdivided into WHO Grades I–IV:

Table 20.1 WHO 2007 classification of nervous system tumours (grades I, II, III, IV).

TUMOURS OF NEUROEPITHELIAL TISSUE

A. Astrocytic tumours

i. Pilocytic astrocytoma (I)
    pilomyxoid astrocytoma (II)
ii. Subependymal giant cell astrocytoma (I)
iii. Pleomorphic xanthoastrocytoma (II)
iv. Diffuse astrocytoma (II)
    fibrillary astrocytoma, gemistocytic astrocytoma
    protoplasmic astrocytoma
v. Anaplastic astrocytoma (III)
vi. Glioblastoma (glioblastoma multiforme, grade IV)
    giant cell glioblastoma, gliosarcoma
vii. Gliomatosis cerebri

B. Oligodendroglial tumours

i. Oligodendroglioma (II)
ii. Anaplastic oligodendroglioma (III)

C. Mixed gliomas (oligoastrocytic tumours)

i. Oligoastrocytoma (II)
ii. Anaplastic oligoastrocytoma (III)

D. Ependymal tumours

i. Subependymoma (I)
ii. Myxopapillary ependymoma (I)
iii. Ependymoma (II)
    cellular, papillary, clear cell, tanycytic
iv. Anaplastic ependymoma (III)

E. Choroid plexus tumours

i. Choroid plexus papilloma (I)
ii. Atypical choroid plexus papilloma (II)
iii. Choroid plexus carcinoma (III)

F. Other neuroepithelial tumours

i. Astroblastoma
ii. Chordoid glioma of 3rd ventricle (II)
iii. Angiocentric glioma (I)

G. Neuronal and mixed neuronal–glial tumours

i. Dysplastic gangliocytoma of cerebellum
    (Lhermitte–Duclos disease, grade I)
ii. Desmoplastic infantile astrocytoma/ganglioglioma (I)
iii. Dysembryoplastic neuroepithelial tumour (I)
iv. Gangliocytoma (I)
v. Ganglioglioma (I, II)
vi. Anaplastic ganglioglioma (III)
vii. Central neurocytoma (II)
viii. Extraventricular neurocytoma (II)
ix. Cerebellar liponeurocytoma (I, II)
x. Papillary glioneuronal tumour (I)
xi. Rosette-forming glioneuronal tumour of 4th ventricle (I)
xii. Paraganglioma (I)

H. Tumours of the pineal region

i. Pineocytoma (I)
ii. Pineal parenchymal tumour of intermediate differentiation (II, III)
iii. Pineoblastoma (IV)
iv. Papillary tumour of the pineal region (II, III)

I. Embryonal tumours

i. Medulloblastoma (IV)
    desmoplastic/nodular medulloblastoma,
    medulloblastoma with extensive nodularity,
    anaplastic medulloblastoma,
    large cell medulloblastoma
ii. CNS primitive neuroectodermal tumour (IV)
    CNS neuroblastoma, CNS
        ganglioneuroblastoma,
    medulloepithelioma, ependymoblastoma
iii. Atypical teratoid/rhabdoid tumour (IV)

TUMOURS OF CRANIAL & PARASPINAL NERVES

Schwannoma (I)
    cellular, plexiform, melanotic
Neurofibroma (I)
    plexiform
Perineurioma
    perineurioma (NOS, I–III),
    malignant perineurioma (II-IV)
Malignant peripheral nerve sheath tumour (MPNST, II–IV)
    epithelioid MPNST, MPNST with mesenchymal differentiation, melanotic MPNST,
    MPNST with glandular differentiation

TUMOURS OF MENINGES

A. Tumours of meningothelial cells

i. Meningioma
    meningothelial (I), fibrous (fibroblastic, I),
        transitional (mixed, I), psammomatous (I), angiomatous (I), microcystic (I), secretory (I), lymphoplasmacyte-rich (I), metaplastic (I), chordoid (II), clear cell (II), atypical (II), papillary (III), rhabdoid (III), anaplastic (malignant, III)

B. Mesenchymal tumours (I–IV)

i. Lipoma
ii. Angiolipoma
iii. Hibernoma
iv. Liposarcoma
v. Solitary fibrous tumour
vi. Fibrosarcoma
vii. Malignant fibrous histiocytoma
viii. Leiomyoma
ix. Leiomyosarcoma
x. Rhabdomyoma
xi. Rhabdomyosarcoma
xii. Chondroma
xiii. Chondrosarcoma
xiv. Osteoma
xv. Osteosarcoma
xvi. Osteochondroma
xvii. Haemangioma
xviii. Epithelioid haemangioendothelioma (II)
xix. Haemangiopericytoma
xx. Anaplastic haemangiopericytoma (III)
xxi. Angiosarcoma
xxii. Kaposi's sarcoma
xxiii. Ewing's sarcoma – PNET

C. Primary melanocytic lesions

Diffuse melanocytosis, melanocytoma, malignant melanoma, meningeal melanomatosis

D. Other neoplasms related to the meninges

Haemangioblastoma (I)

LYMPHOMAS AND HAEMATOPOIETIC NEOPLASMS

Malignant lymphomas, plasmacytoma, granulocytic sarcoma

GERM CELL TUMOURS

Germinoma
Embryonal carcinoma
Yolk sac tumour
Choriocarcinoma
Teratoma
    mature, immature, teratoma with malignant transformation
Mixed germ cell tumour

TUMOURS OF THE SELLAR REGION

Craniopharyngioma (I)
    adamantinomatous, papillary
Granular cell tumour (I)
Pituicytoma (I)
Spindle cell oncocytoma of adenohypophysis (I)

METASTATIC TUMOURS (IV)

- Pilocytic astrocytoma (WHO Grade I);
- Diffuse astrocytoma (WHO Grade II);
- Anaplastic astrocytoma (WHO Grade III); and
- Glioblastoma multiforme (GBM; WHO Grade IV).

Diffuse astrocytomas (WHO Grade II) tend to develop within the cerebral hemispheres, especially in the frontal and temporal lobes. This tumour with its subtypes fibrillary, gemistocytic, i.e. large swollen cytoplasm and the very rare protoplasmic variant, is a slowly growing tumour that typically affects young adults and has an intrinsic tendency to progress into higher grades (WHO Grades III and IV). This process, known as malignant transformation, distinguishes WHO Grade II tumours from WHO Grade I tumours with more stable histology which have a considerably better prognosis.

The characteristic morphology of the cells of WHO Grade II astrocytomas resembles well-differentiated astrocytes, embedded in a fibrillary or microcystic matrix. Mitotic activity is typically absent and there is no microvascular proliferation or necrosis. The gemistocytic subtype is particularly prone to progress to high-grade glioma.

The high-grade anaplastic astrocytoma (WHO Grade III) shows an infiltrative behaviour with focal or generalized increase in proliferative potential. These tumours may progress from a low-grade astrocytoma but they are also seen at first biopsy without evidence for an underlying low-grade lesion. Compared with WHO Grade II astrocytomas, anaplastic astrocytomas are characterized by increased cellularity, higher mitotic activity, more distinct nuclear atypia but no necrosis or vascular proliferation. They also have an intrinsic propensity to progress to GBM.

GBM is the most frequent malignant primary CNS tumour, accounting for about 30% of all primary brain tumours and 60% of all gliomas. This highly malignant astrocytic tumour preferentially affects older adults (peak incidence 60–70 years) and arises in the cerebral hemispheres, most commonly temporal, parietal and frontal lobes. Typical histological features include poorly differentiated, often highly pleomorphic glial tumour cells with marked nuclear atypia and brisk mitotic activity. Necrosis and/or microvascular proliferation are essential for diagnosis and in most cases both are present. GBM can vary considerably in their histological appearance, ranging from highly cellular and monotonous to very variable and heterogeneous. This may present a challenge when histological diagnosis is based on small needle biopsies.

Genetic studies suggest that primary (*de novo*) and secondary (evolving from low-grade gliomas by multi-step progression) GBM are different entities. Primary GBMs arise in older patients and are strongly associated with amplification and over-expression of the epidermal growth factor receptor gene (*EGFR*), and show increased murine double minute 2 promoter (*MDM2*) oncogene activity, while secondary GBMs arise from previous low-grade gliomas, occur in younger individuals and are associated with early p53 loss and over-expression of platelet-derived growth factor gene (*PDGF*). Both primary and secondary GBMs show frequent loss of the phosphatase and tensin homologue (*PTEN*) gene.

Other astrocytic tumours

Pilocytic astrocytomas (WHO Grade I) are most common in children but also occur in young adults. They have a predilection for the cerebellum. They also occur in locations close to the midline such as the hypothalamus, thalamus, optic chiasm and brainstem. In adults they may be also found in the cerebral hemispheres.

Pleomorphic xantho-astrocytomas are found most commonly in the cerebral hemispheres, particularly within the temporal lobes.

Subependymal giant cell astrocytomas occur most commonly in the lateral wall of the third ventricle, almost exclusively in patients with tuberous sclerosis.

Brainstem gliomas are rare, usually occur in children and are associated with a dismal prognosis with a median survival of less than 1 year. In adults they behave typically as low-grade gliomas with median survival measured in years rather than months but occasionally present as high-grade gliomas.

Optic nerve gliomas are usually pilocytic astrocytomas presenting in children. These behave indolently. In adults, however, these are highly aggressive tumours associated with a survival of a few weeks.

Oligodendrogliomas

These account for 10–15% of all gliomas and occur predominantly in adults. Despite their name, their origin from oligodendrocytes or their precursors has not been proven. They comprise a continuous spectrum ranging from well-differentiated tumours to highly malignant neoplasms. The WHO grading system distinguishes two malignancy grades: Grade II oligodendrogliomas are slowly growing, well-defined hemispheric tumours composed of rounded homogenous nuclei. Paraffin embedding results in a reproducible artefact, the formation of clear cytoplasm around the nuclear giving rise to a perinuclear halo, often referred to as ‘fried egg’ or ‘honeycomb’ cells. Further typical features are branching capillaries and calcification. High-grade features are increased tumour cell density, mitotic activity, presence of microvascular proliferation and necrosis. These are graded WHO Grade III rather than IV.

Some gliomas have intermixtures of astrocytic and oligodendroglial cellular elements and are appropriately called oligoastrocytomas or mixed gliomas. Like astrocytomas and oligodendrogliomas they have a propensity to transform into high-grade gliomas.

Molecular genetics of oligodendroglioma

The discovery that loss of heterozygosity (LOH) of chromosomal arms 1p and 19q in anaplastic oligodendroglioma was associated with a prolonged and durable response to chemotherapy marked an important step forward in the treatment of brain tumours. Numerous studies on this genotype–phenotype correlation have subsequently shown that:

1 LOH of 1p/19q occurs in about 70% of oligodendrogliomas but is rare in astrocytomas (<10%). Pure oligodendrogliomas have more frequently combined 1p/19q LOH than oligoastrocytomas (40%).
2 Solitary loss of 1p is rare.
3 Solitary loss of 19q is uncommon in oligodendrogliomas (1%) but more frequently seen in oligoastrocytomas (18%) and can also occur in other glial tumours.
4 1p/19q LOH is an early event in oligodendroglioma and is retained during tumour progression.
5 Combined LOH of 1p/19q is related to survival. This improved prognosis (and response to radiotherapy and chemotherapy) is present whether observed at initial diagnosis or at recurrence. Oligodendrogliomas with 1p/19q LOH also tend to progress more slowly at recurrence.

Ependymomas

These slowly growing tumours present at any age but are most common in the first and second decades of life. They account for 4–9% of neuroepithelial tumours. They occur at any site along the ventricular system, most commonly in the fourth ventricle in children and the cervical spine or conus medullaris in adults. They are well-defined but can encase peripheral nerves when they grow laterally from the fourth ventricle. Characteristic histological features are the formation of pseudorosettes, the concentric arrangement of ependymal cells around a vessel. Fibrillary glial processes of ependymal cells radiate to centrally located vessels and form a nuclei-free area, which creates this distinctive histological appearance. There are further variants of ependymoma which are named according to prevailing features such as cellular, papillary, clear cell and tanycytic but these distinctions have little or no clinical importance. A distinct variant is the WHO Grade I myxopapillary ependymoma of the spinal filum terminale.

Grade II ependymomas are well defined, show monomorphic nuclei and rare mitotic activity while Grade III (anaplastic) ependymomas show increased cellularity, increased mitotic rate and often vascular proliferation and necrosis.

In adults, ependymomas account for about 2% of all intracranial tumours and are associated with a high survival rate compared with other glial tumours (5 and 10-year survival 85% and 76%, respectively). Overall survival correlates well with histological grade, extent of resection, age and performance status.

Medulloblastomas

These malignant invasive embryonal tumours arise in the cerebellum, typically in children, declining sharply in incidence after the age of 15 years. They are the most common malignant brain tumour in children. Macroscopically, they vary in growth pattern, ranging from firm and discrete to soft and less well-defined tumours. They mostly arise in the cerebellar vermis, but with increasing age tend to develop within the cerebellar hemispheres. There is increasing experimental evidence that medulloblastomas originate from the external granular layer (EGL) of the cerebellum. Histologically, medulloblastomas vary in their appearance. The undifferentiated or classic medulloblastoma is the most common form, characterized by densely packed, round or oval cells with a high nucleus to cytoplasm ratio and showing neuroblastic rosettes formed by circular arrangements of tumour cells around a virtual centre. The nodular or desmoplastic variant is characterized by extensive formation of nodules that show neuronal differentiation and are surrounded by thin collagenous septae and undifferentiated cells. A more recently defined entity is the large cell anaplastic variant (approximately 4%) composed of markedly irregularity and atypia, frequent mitoses and apoptosis. This variant is associated with a particularly poor prognosis. Medulloblastoma can show a variable degree of differentiation into neuronal, and rarely glial, ependymal, muscular (medullomyoblastoma) or melanocytic (melanotic medulloblastoma) lineages.

Molecular genetics and histogenesis of medulloblastoma

There is increasing evidence that genes involved in normal developmental processes may also contribute to tumorigenesis if mis-expressed. Hence, pathways involved in the expansion of EGL precursor cells are also involved in the pathogenesis of medulloblastomas. The Sonic Hedgehog (Shh)–Patched (Ptch) signalling pathway is a major mitogenic regulator of EGL progenitor cells. Mutations of the key mediators of the Shh–Ptch pathway (PTCH, SUFU and SMOH) have been described in 25% of sporadic human medulloblastomas. Other pathways implicated in medulloblastoma pathogenesis include the *notch* and the *wnt* signalling cascades.

Meningiomas

These common extra-axial intracranial tumours grow slowly, are well demarcated and do not usually infiltrate the brain. They originate from meningothelial cells which are most abundant in the arachnoid villi and occasionally from the cranio-spinal arachnoid. They are most common in elderly patients with a peak in the sixth and seventh decade, with a slight predominance for female gender. Generally they arise within intracranial, orbital and spinal cavities, favouring the parasagittal area, convexities, sphenoid wing, tuberculum sellae, olfactory groove and tentorium. Histologically, meningiomas are very heterogeneous. The most common meningioma types are meningothelial, fibrous/fibroblastic, transitional and psammomatous (abundant whorls with calcifications), and more than 10 additional variants are listed in the WHO classification. Most of them correspond to WHO Grade I and behave similarly. Atypical features in meningioma are increased mitotic activity (>4 mitoses per 10 high power field (HPF)), patternless growth and necrosis corresponding to WHO Grade II (atypical) or WHO Grade III (anaplastic meningioma), when there are greater than 20 mitoses per 10 HPF. The higher grade meningiomas have a propensity for recurrence, as one might expect. In rare cases they behave almost as aggressively as malignant gliomas.

Histology of less common tumours

The histological features of four less common tumours are illustrated in Plate 20.3. Clinical details are described below.

The schwannoma shown in Plate 20.3 has typical arrangements of pallisading nuclei against a fibrillary background, forming so-called Verocay bodies. Around those structures are loosely textured tumour areas, so-called Antoni B areas (a). Reticulin silver stain visualize the dense pericellular basement membranes (b). S100 immunohistochemistry typically shows nuclear and cytoplasmic staining in schwannoma (c).

Chordomas are characterized by chords of cells arranged against a background of myxoid stroma (d). Typical immunohistochemical profile includes positive labelling of the tumour cells with cytokeratin (e) and S100 protein (f).

Lymphomas are arranged in dense patternless sheets and infiltrate adjacent brain tissue diffusely and also in characteristic peri-vascular arrangements, shown in (g). Most primary intracerebral lymphomas are of B-cell type and are positive for the B-cell marker CD20, as shown here (h). These tumours are highly malignant and exhibit a very high mitotic index; Ki67 proliferation can be as high as 90%. The lymphoma shown here has a proliferation index of approximately 50% (i).

Pineoblastomas belong to the group of primitive neuroectodermal tumours and arise in the pineal region. Histological features include the formation of neuroblastic rosettes as shown in (j). In intra-operative smear preparations, these tumours typically spread out to monolayers with fine synaptic networks (k). They almost invariably express the neuronal marker synaptophysin, as shown in (l).

Imaging of common brain tumours

Structural brain imaging

Magnetic resonance imaging (MRI) is the preferred modality for structural imaging of brain tumours and provides better soft tissue differentiation and tumour delineation than computed tomography (CT). CT demonstrates tumour calcification better than MRI: on MRI the signal may be difficult to distinguish from intra-tumoural haemorrhage. Structural MRI of brain tumours should include T2-weighted (T2) fluid-attenuated inversion recovery (FLAIR) and T1-weighted (T1) images before and after injection of gadolinium. The general imaging and macroscopic appearance of common intracranial tumours are shown in Plates 20.4 and 20.5.

Most tumours appear hypodense on CT, hypointense on T1 and hyperintense on FLAIR and T2 MRI. Highly cellular tumours such as lymphomas and primitive neuro-ectodermal tumours have a decreased water content and therefore appear hyperdense on CT and relatively hypointense on T2 MRI. Intra-tumoural haemorrhage and tumour calcification appear usually hypointense on T2 images and become more conspicuous on T2* gradient echo images. Hyperintensities on T1 images can be because of haemorrhage, calcification, melanin or fat.

Contrast enhancement on CT or MRI is either seen in highly vascular extra-axial tumours such as meningiomas (Figure 20.1) or in intra-axial tumours disrupting the blood–brain barrier such as cerebral lymphomas (Figure 20.2).

Enhancement is generally a feature of high-grade tumours such as high-grade gliomas and metastases but can also be present in certain low-grade tumours, such as pilocytic astrocytomas and WHO Grade II oligodendrogliomas. The visibility of contrast enhancement on MRI can be improved by magnetization transfer imaging, by doubling or tripling the gadolinium dose or by using high relaxivity gadolinium compounds.

Physiological imaging

Diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), MR spectroscopy (MRS) and functional MRI (fMRI) provide information about physiological and metabolic processes not seen with standard MRI. Much of the recent progress in tumour imaging is based on these physiological methods, which are now being increasingly implemented in clinical practice. More recently, CT perfusion imaging has emerged as another technique to assess the relative cerebral blood volume (rCBV) and permeability changes in brain tumours. Compared with MR perfusion techniques it brings limited diagnostic focus to the region of interest despite progress in multi-detector technology.

MR perfusion imaging

Dynamic susceptibility-weighted contrast-enhanced (DSC) MRI is the most widely used technique of PWI in brain tumours and analyses a series of images acquired during the first pass of an intravenously injected bolus of gadolinium (Plate 20.6).

rCBV measurement provides an indirect measure of tumour neovascularity. This correlates closely with angiographic and histological markers of tumour vascularity and the expression of vascular endothelial growth factor (VEGF). High-grade glial tumours tend to have higher rCBV values than low-grade tumours and PWI significantly increases the specificity and sensitivity of conventional MRI in the classification of gliomas. Maps of rCBV can also be a useful adjunct for stereotactic tumour biopsies, directing tissue sampling towards areas of maximal angiogenesis.

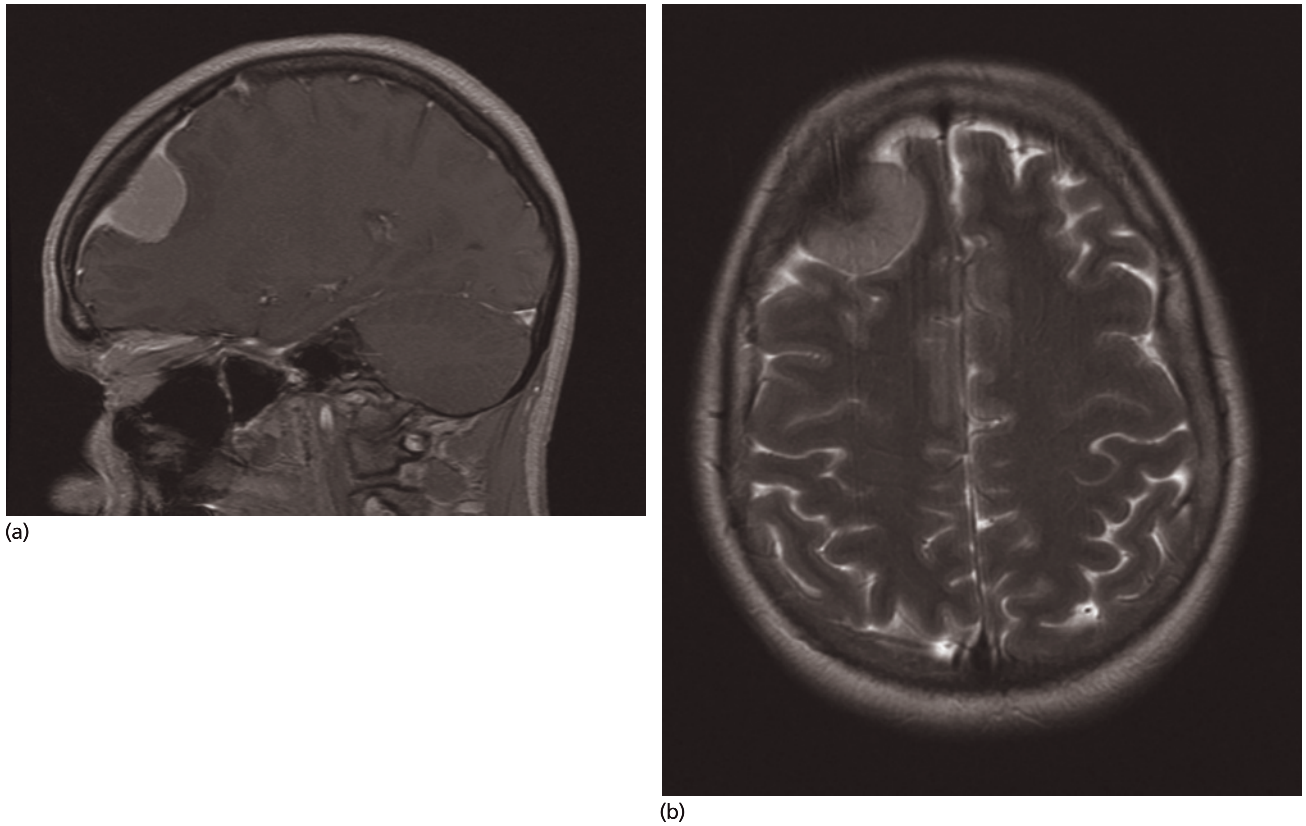


Figure 20.1 (a) Sagittal contrast-enhanced T1 images of a meningioma showing typical appearances of an enhancing durally based mass associated with bony hyperostosis and a dural tail sign. (b) Corresponding axial T2 images demonstrating a grey matter iso-intense mass displacing the frontal lobe with hyperostosis but no associated oedema.

Permeability imaging (K^{trans})

Microvascular permeability of brain tumours can be quantified by measuring the transfer coefficient K^{trans} which is influenced by endothelial permeability, vascular surface area and flow. This can be measured using a T1 steady state or a first pass T2* gradient echo technique. The former has a higher spatial resolution and is more accurate but requires longer acquisition times and more complicated post-processing; the latter can be combined with DSC perfusion imaging. K^{trans} correlates with tumour grade and is probably more sensitive than rCBV measurements for glioma grading.

MR diffusion imaging

DWI measures Brownian motion of water molecules within tissue. Images are obtained by measuring the signal loss typically on MR T2 images following the application of diffusion gradients (Figure 20.3). The signal loss depends on several factors including the gradient strength and apparent diffusion coefficient (ADC) which describes water diffusion within tissue. The more mobile the water molecules, the higher the ADC and the greater the signal loss on DWI. DWI are still influenced by T2 effects, which can lead to artefacts known as T2 shinethrough, whereas ADC maps provide a quantitative representation of water movement. Therefore, highly cellular tumours, e.g. lymphoma, which are associated with limited water mobility, show up as dark on ADC and bright on DWI.

Visual inspection of DWI has a limited role in the diagnosis of brain tumours. However, it may be valuable to identify lesions with severely restricted diffusion, such as acute infarcts or abscesses that can occasionally mimic brain tumours on standard MRI but which appear as high-intensity lesions on DWI (Figure 20.4).

ADC measurements provide more detailed information about brain tumours and have been shown to correlate with the histological cell count and with the presence of hydrophilic substances in the tumour matrix. Diffusion tensor imaging (DTI) provides additional information about the direction of water diffusion. The tendency of water to move in some directions more than others is called anisotropy and can be quantified using parameters such as fractional anisotropy (FA). Compact white matter tracts normally show a high degree of anisotropy which can be lost if they are infiltrated by tumour cells destroying ultrastructural boundaries. Another application of DTI is tractography, which depicts white matter tracts and their connections on direction-encoded colour images. Tractography is useful in the pre-operative assessment of brain tumours and can differentiate between displacement and infiltration of white matter tracts.

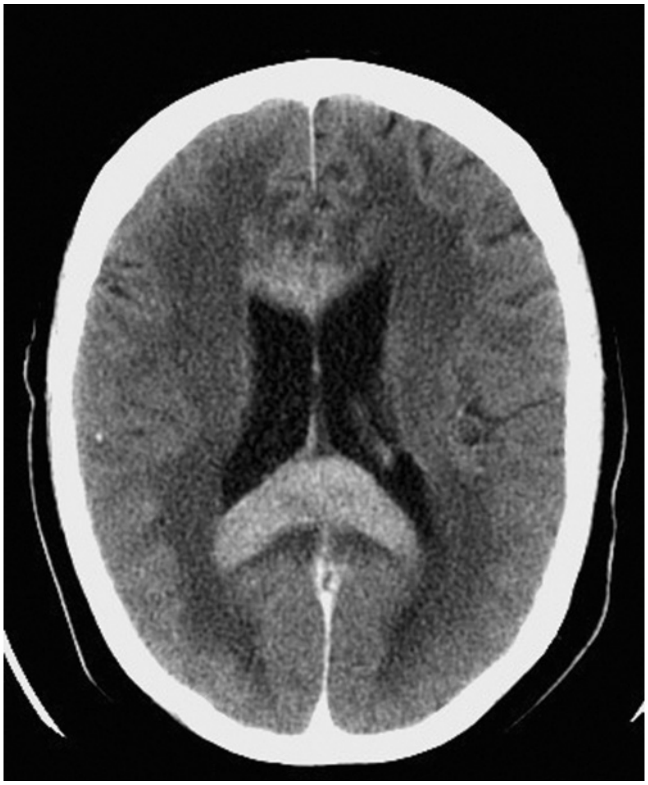


Figure 20.2 Contrast-enhanced computed tomography (CT) of a patient with cerebral lymphoma demonstrating an enhancing mass infiltrating the genu and splenium of the corpus callosum.

MR spectroscopy

Proton MR spectroscopy (MRS) analyses aspects of the biochemical make-up of a brain tumour and provides semi-quantitative information about major metabolites. A common pattern in brain tumours is a decrease in *N*-acetyl-aspartate (NAA), a neurone-specific marker, with an increase in choline (Cho), lactate and lipids. The concentration of Cho is a reflection of the turnover of cell membranes and is more elevated in regions with a high neoplastic activity (Figure 20.5). Lactate is the end product of nonoxidative glycolysis and a marker of hypoxia in tumour tissue, now recognized as a major promoter of tumour angiogenesis and invasion. Lactate probably indicates viable but hypoxic tissue, whereas mobile lipids reflect tissue necrosis and breakdown of cell membranes. MRS with a short echo times (20–40 ms) can demonstrate additional metabolites, such as myoinositol, glutamate and/or glutamine and mobile lipids but is hampered by baseline distortion and artefactual NAA peaks. Chemical shift imaging (CSI) or MRS provides spectral information across a whole tumour region and has been used to inform surgical biopsy targets.

Functional MRI

Blood oxygen level-dependent (BOLD) imaging detects changes in regional cerebral blood flow during various forms of brain activity (Chapter 3). Paradigms using motor tasks, language and speech production and memory are able to show recruitment of activation within relevant cortical areas. The main use of fMRI in tumour imaging is the pre-operative localization of eloquent cortical regions Plate 20.7 which may have been displaced,

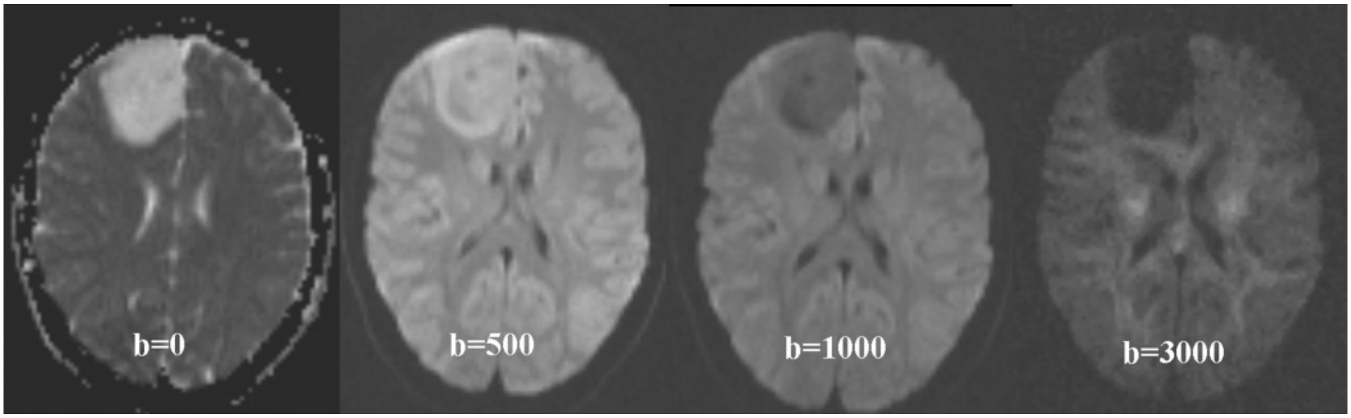


Figure 20.3 Diffusion-weighted images of a frontal low-grade glioma. With increasing diffusion weighting (higher b values) progressive signal loss occurs, first in areas of high water mobility, such as cerebrospinal fluid (CSF) and subsequently also in the tumour.

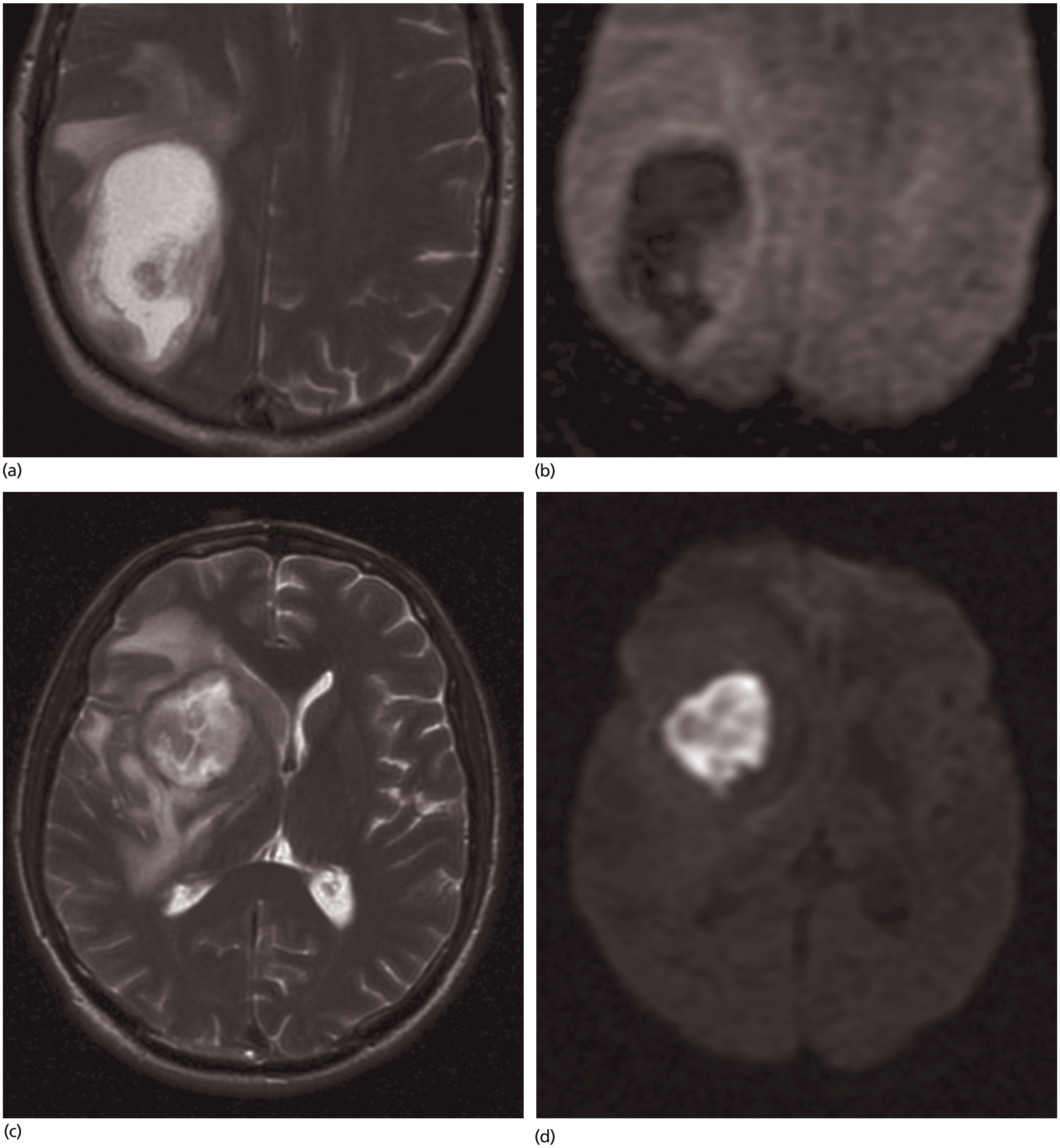
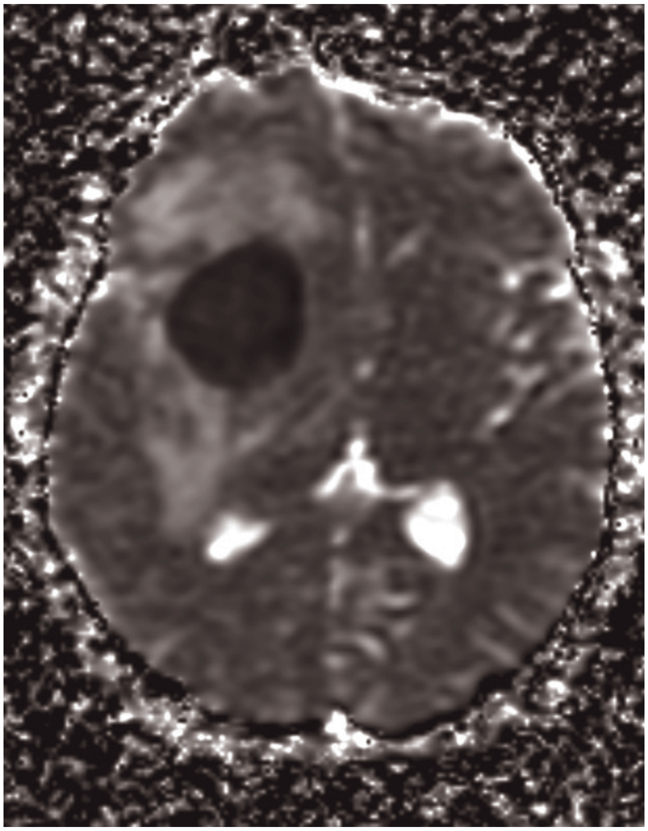


Figure 20.4 (a) T2 image of a cystic high-grade glioma with a hyperintense centre, irregularly thickened rim and vasogenic oedema. (b) The diffusion-weighted image shows loss of signal in the central portion, typical of a necrotic centre in a cystic neoplasm. (c) T2 image of another, undiagnosed cystic frontal lobe mass lesion with a hyperintense centre and surrounding vasogenic oedema. (d) Diffusion-weighted image shows markedly restricted diffusion in this case, typical of an abscess confirmed at biopsy. (e) On the corresponding ADC map the abscess cavity appears dark and vasogenic oedema appears bright.



(e)

Figure 20.4 *Continued*

distorted or compressed by the tumour. This can both improve the safety of surgery and allow for a more radical resection. Ideally, fMRI should be combined with MR tractography in order to minimize intra-operative injury to white matter tracts connected to eloquent cortical areas.

Imaging of neuroepithelial tumours

The focus here is on the imaging appearances of the more common brain tumours.

Pilocytic astrocytomas

Pilocytic astrocytomas, the most common WHO Grade I astrocytomas, are well-circumscribed, potentially resectable lesions with a low proliferative potential and a predilection for the posterior fossa, optic nerves and hypothalamus. Pilocytic atrocytomas usually have a significant cystic component and show mural enhancement which can be nodular or ring-like (Figure 20.6). Infratentorial pilocytic astrocytomas in adults may be mistaken for haemangioblastomas.

Diffuse astrocytomas

Diffuse astrocytomas (WHO Grade II) typically occur in the cerebral hemispheres of young adults, involve cortex and white matter and have less well-defined borders than pilocytic astrocytomas. Mass effect is variable and contrast enhancement usually absent. They appear isodense or hypodense on CT which shows areas of calcification in up to 20%. On MRI, diffuse astrocytomas are hypointense or isointense on T1 images and hyperintense on T2 and FLAIR images, which provide the best contrast between tumour and normal brain tissue (Figure 20.7). WHO Grade II astrocytomas show a low mitotic activity but have a propensity to progress to a higher histological grade, as suggested by the development of new gadolinium enhancement (Figure 20.7d).

Anaplastic astrocytomas

Anaplastic astrocytomas (WHO Grade III) are high-grade gliomas which usually show contrast enhancement and more extensive infiltration of the peri-tumoral tissues than WHO Grade II lesions. They may also be accompanied by vasogenic oedema. In many cases, however, it is not possible to distinguish radiologically between Grade II and Grade III tumours, i.e. the absence of enhancement does not rule out a high-grade tumour.

Pleomorphic xanthoastrocytomas

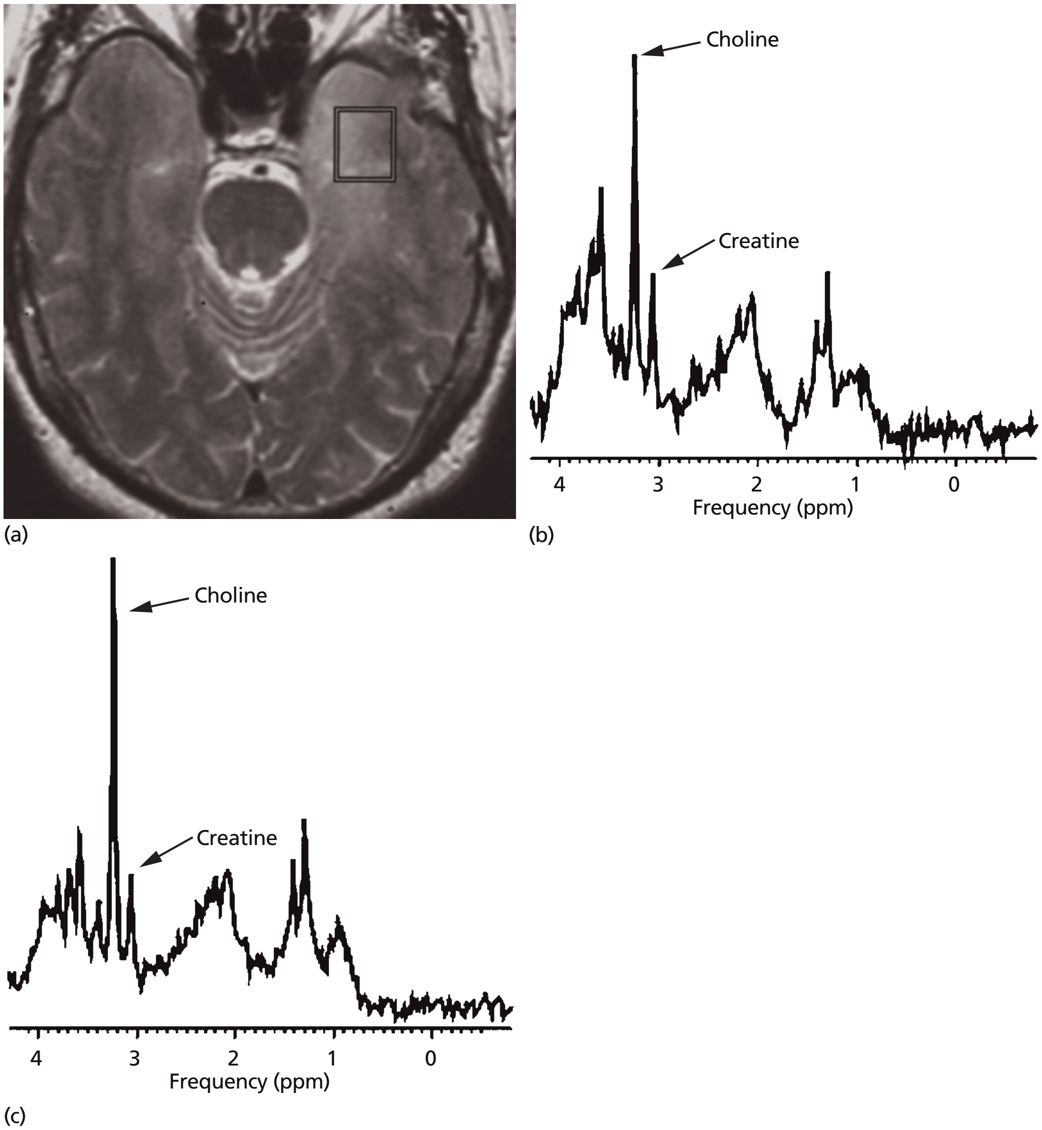
Pleomorphic xanthoastrocytoma (WHO Grade II or III) is an astrocytic tumour that arises near the surface of a cerebral hemisphere and is frequently cystic. The tumour may enhance strongly and is usually associated with little or no oedema. Despite its fat content, it is T1-hypointense and T2-hyperintense on MRI.

Glioblastoma multiforme

Glioblastoma multiforme (GBM; WHO Grade IV) is a poorly differentiated, highly pleomorphic tumour with vascular proliferation and necrosis. Vasogenic oedema and contrast enhancement are more extensive than in anaplastic (WHO Grade III) astrocytomas. Tumour necrosis appears as intra-tumoural areas of approximately CSF signal intensity, frequently surrounded by irregularly enhancing regions of active mitosis (Figure 20.8). Intra-tumoural haemorrhage with T1 hyperintense and T2 hypointense areas contributes to the heterogeneous MR appearance of GBMs.

Oligodendrogliomas

Oligodendrogliomas (WHO Grades II and III) are diffusely infiltrating neoplasms found almost exclusively in the cerebral hemispheres, most commonly in the frontal lobes and typically involving subcortical white matter and cortex. Both low- and high-grade oligodendroglial tumours express pro-angiogenic mitogens and may contain regions of increased vascular density with finely branching capillaries which have a chickenwire appearance seen on contrast-enhanced MRI and PWI. Up to 90% of oligodendrogliomas contain calcification visible on CT, central, peripheral or ribbon-like. Contrast enhancement is variable and often heterogeneous. It is a much less reliable indicator of tumour grade than in astrocytic tumours.


Choline
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Frequency (ppm)
(c)

Figure 20.5 (a) Single voxel MR spectroscopy of a temporal lobe tumour demonstrating region of interest. (b) Initial MR spectrum of a low-grade primary tumour showing a high choline : creatine ratio. (c) MR spectrum 6 months later, following transformation into a high-grade tumour shows a further increase in the choline peak compared to the baseline study (from 1.6 to 3.1 mmol/L).

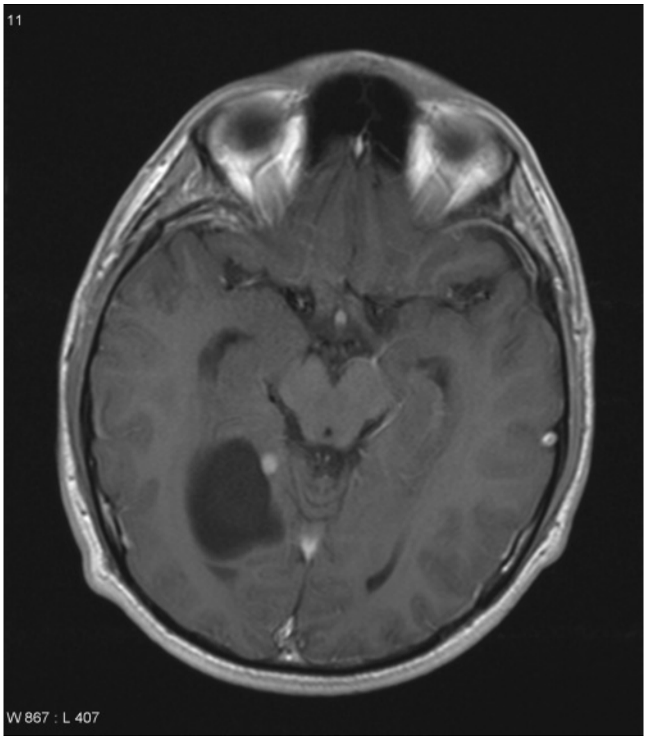


Figure 20.6 Contrast-enhanced T1 image of an adult patient with a pilocytic astrocytoma showing a cystic lesion with a small enhancing mural nodule anteromedially.

Oligodendrogliomas with intact 1p/19q (see above) tend to have a more homogenous signal on T1 and T2 images with sharper borders than tumours with 1p/19q deletions.

Ependymomas

Ependymomas (WHO Grades II and III) in the brain are usually intraventricular, although extraventricular rests of ependymal cells may also give rise to hemisphere tumours. They are well-demarcated lobulated mass lesions with calcification on CT in over 50% and mixed signal intensity on MRI (predominantly hyperintense on T2 and isointense to hypointense on T1 images). Enhancement is mild to moderate and often heterogeneous.

Physiological imaging and grading of glial tumours

Distinguishing between astrocytomas and oligodendrogliomas

PWI and DWI can help to differentiate between low-grade astrocytic and oligodendroglial tumours. WHO Grade II oligodendrogliomas have significantly higher rCBV than WHO Grade II astrocytomas with median values of 3.68 versus 0.92, respectively, which concurs with the histological findings of increased vascular density in oligodendrogliomas (Plate 20.8). In addition, rCBV of oligodendrogliomas appears dependent on their genotype, the loss of 1p/19q being associated with significantly higher rCBV values. Measurement of the ADC, using a whole tumour histogram analysis, appears promising for the differentiating between astrocytomas and oligodendrogliomas. The latter have significantly lower ADC values than astrocytomas (Plate 20.8 and Figure 20.9), reflecting a higher cellular density and differences in tumour matrix composition.

Distinguishing between low-grade and high-grade gliomas

Advanced MRI can help distinguish between low-grade and high-grade gliomas. Formation of new blood vessel (angiogenesis) represents an important aspect of glial tumour progression and mean maximum rCBV values correlates closely with histological grades. PWI is also valuable (Plate 20.9) DWI can be disappointing in helping to differentiate high-grade from low-grade gliomas (Figures 20.10 and 20.11).

Physiology-based MRI of peri-tumoural tissue

Investigation of peri-tumoural regions with physiology-based MR techniques may be of similar importance to the radiological assessment of the tumour itself. Differences in the peri-tumoural tissues of low-grade and high-grade gliomas have been demonstrated with DWI, PWI and MRS. The peri-tumoural regions of high-grade gliomas show a more marked decrease in ADC, FA and NAA and increase in rCBV compared to low-grade tumours. This is a reflection of the more invasive nature of these tumours which infiltrate the adjacent brain tissue along vascular channels leading to an increase in rCBV, destroy ultrastructural boundaries to produce a decrease both in ADC and FA and replace normal brain tissue with a corresponding fall in NAA. Metastases, on the other hand, are surrounded by pure vasogenic oedema that contains no infiltrating tumour cells. Peri-tumoural regions in metastases typically show neither increase in rCBV nor decrease in FA.

Tumours of predominantly neuronal cell origin

Gangiogliomas and gangliocytomas

Gangiogliomas and gangliocytomas (WHO Grade I) are slow-growing tumours that grow preferentially within the temporal lobes of children and young adults. CT and MRI show peripherally located mixed solid and/or cystic lesions that commonly calcify. Enhancement can be variable and is often peripheral.

Central neurocytomas

Central neurocytomas (WHO Grade I) occur predominantly in the second and third decades of life and are the most common masses within the lateral ventricles in this age group. They typically arise from the septum pellucidum and occupy the frontal horns and bodies of the ventricles and sometimes extend through the foramen of Monro. Obstructive hydrocephalus is common. CT frequently demonstrates calcification and small cysts. MRI shows a heterogeneously enhancing mass with septated cysts and isointense grey matter nodules with susceptibility artefact from calcification.

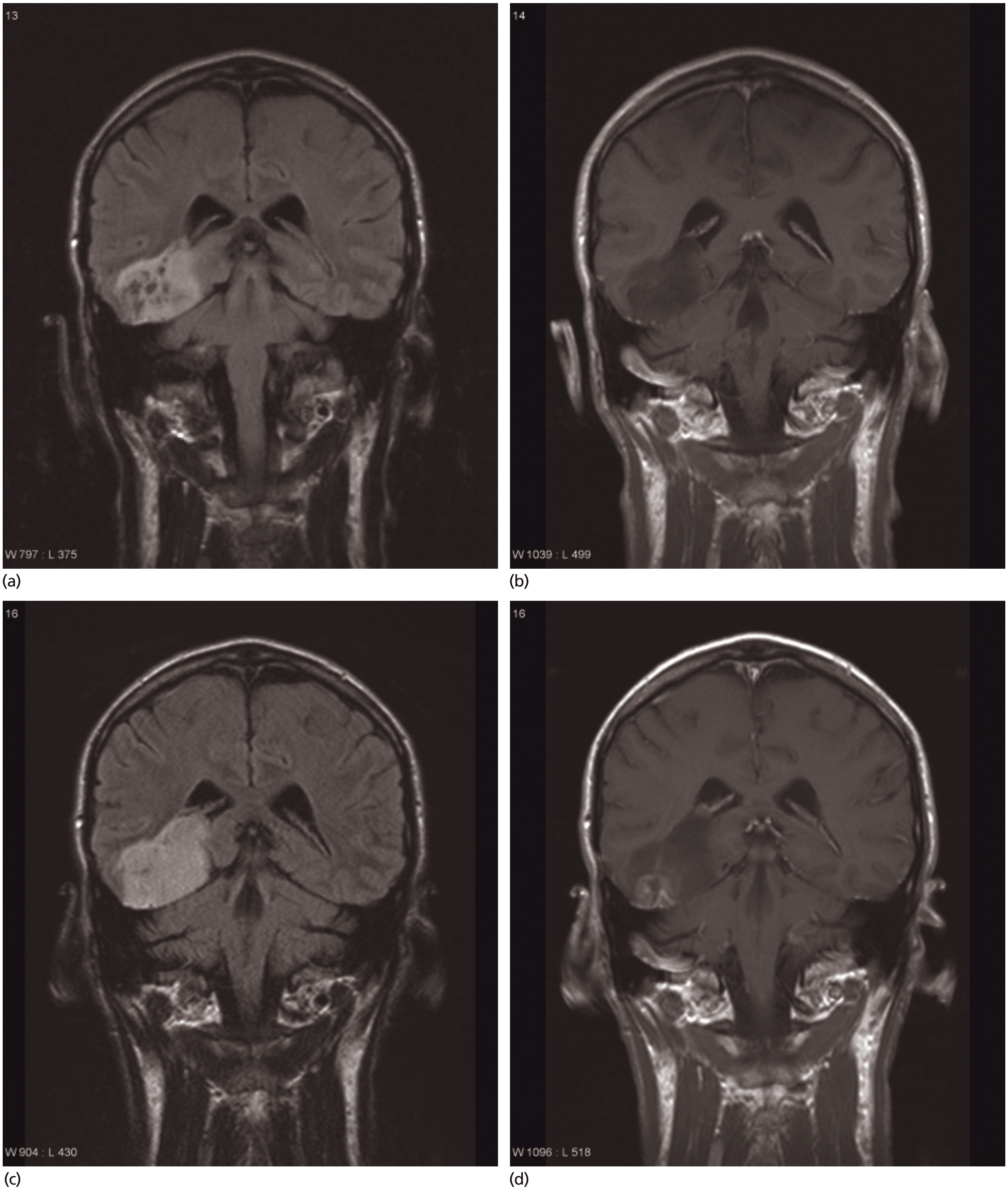


Figure 20.7 (a) FLAIR image of a WHO Grade II astrocytoma presenting as well-demarcated hyperintense temporal lobe mass containing small cysts. (b) Corresponding contrast-enhanced T1 image does not demonstrate any pathological enhancement. (c) 12 months' follow-up FLAIR image demonstrates tumour enlargement with disappearance of cystic elements. (d) 12 months' follow-up contrast-enhanced T1 image: pathological enhancement at the inferior aspect of tumour. Repeat biopsy confirmed progression to WHO Grade III astrocytoma.

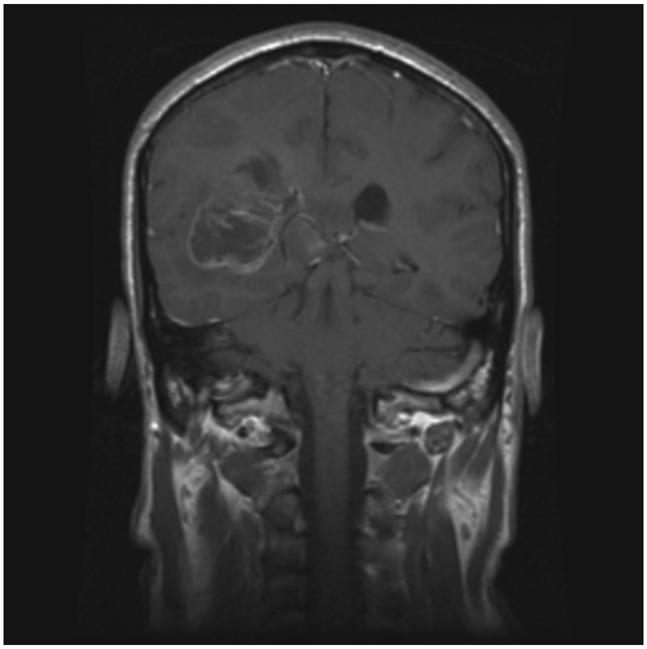


Figure 20.8 Right, deep temporal glioblastoma multiforme (MR T1W).

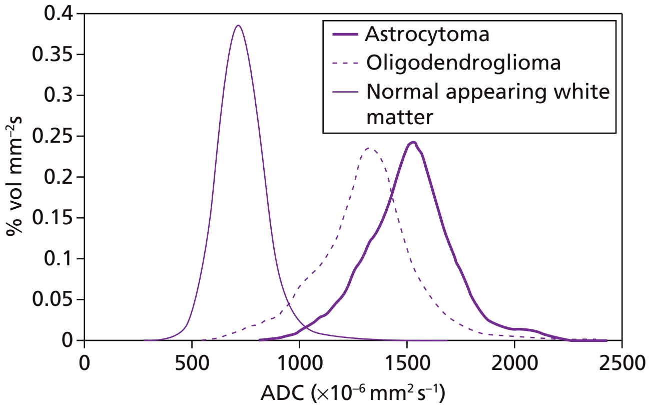


Figure 20.9 Whole tumour ADC histograms of a low-grade astrocytoma and a low-grade oligodendroglioma. Both have higher ADC values than normal white matter. Histogram of the oligodendroglial tumour is shifted to the left compared to histogram of the astrocytic tumour, indicating overall lower ADC values in the former.

Dysembryoplastic neuroepithelial tumours

Dysembryoplastic neuroepithelial tumours (DNET) are WHO Grade I and usually located in the cerebral cortex. Intractable complex partial seizures are common. On CT, DNET are usually hypodense. On MRI they are T1-hypointense and T2-hyperintense. Small intra-tumoural cysts may cause a bubbly appearance; calcification is seen in about 25% and enhancement is uncommon. Thinning of the overlying bone is present in approximately half of the cases, reflecting the extremely slow growth of these tumours which allows bone remodelling to occur (Figure 20.12).

Choroid plexus tumours

Choroid plexus tumours are either WHO Grade I or III, i.e. papillomas or carcinomas. Choroid plexus papillomas are much more common than carcinomas. The location and incidence of choroid plexus papillomas varies with age. They are more common in childhood, presenting as a cauliflower-like mass in the trigone of the lateral ventricle. In adults, papillomas occur predominantly in the fourth ventricle. CT shows an isodense to hyperdense mass with punctate calcification and homogenous enhancement. On MRI the papillomas appear as lobulated, intraventricular masses of heterogeneous, predominantly intermediate signal intensity on T1 and T2 images with intense contrast enhancement.

Medulloblastomas and other primitive neuro-ectodermal tumours

WHO Grade IV tumours of neuro-ectodermal origin include medulloblastomas and other primitive neuro-ectodermal tumours (PNETs). Medulloblastomas usually arise in the cerebellar midline in children and the cerebellar hemispheres in adults. In contrast, PNETs are usually supratentorial. The high nuclear : cytoplasmic ratio of both these tumours is responsible for their hyperdense appearance on CT and hyperintense appearance on DW images. A three- to fourfold elevation of Cho and lipid on MRS is caused by their intense cellularity and cell turnover. PNETs enhance and have a propensity for dissemination in the subarachnoid space with leptomeningeal deposits. Staging of these tumours requires contrast-enhanced MRI of the entire neuraxis.

Primary CNS lymphomas

PCNSL usually presents as a single, lobulated enhancing mass, often abutting an ependymal (Figure 20.2) or meningeal surface. Occasionally, PCNSL are multiple. Enhancement is uniform in immunocompetent patients but tends to be ring-like in immunocompromised patients because of areas of central necrosis. The high cellular density of PCNSL accounts for its hyperdensity on CT and hypointensity on T2 MRI. The ADC of PCNSL is lower than in gliomas or toxoplasmosis which is an important differential diagnosis in immunocompromised patients (Figure 20.13). PCNSL grows in an angiocentric fashion around existing blood vessels without extensive new vessel formation. PWI therefore shows only a modest increase in rCBV, much less marked than in high-grade gliomas where angiogenesis is a prominent feature.

Metastases

Brain metastases most commonly arise from carcinoma of the lung, breast and malignant melanoma. Most metastases enhance strongly with contrast media, either uniformly or they are seen as ring-like structures if the metastasis has outgrown its blood supply. Metastases are frequently associated with vasogenic oedema, often disproportionate to the size of the tumour.

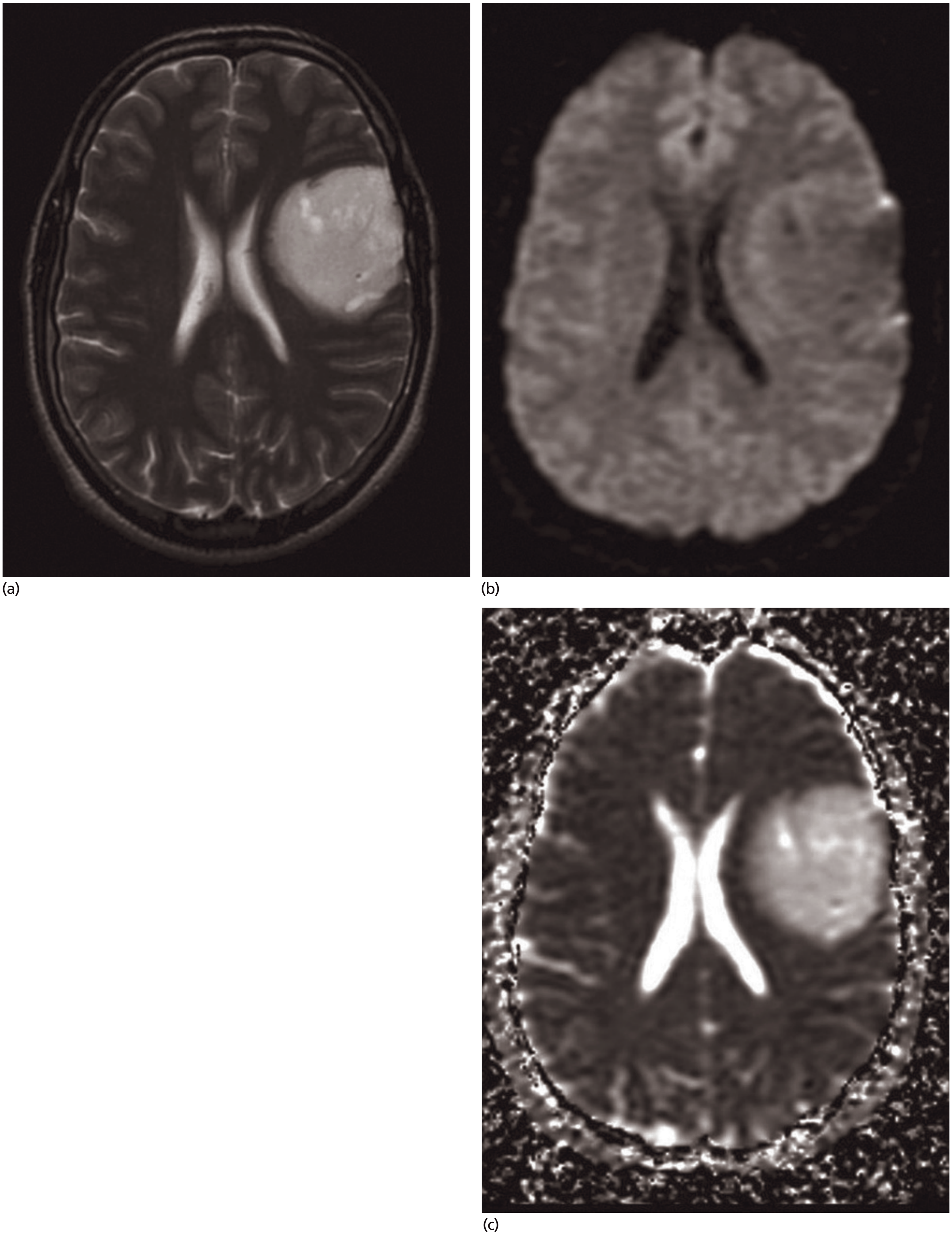


Figure 20.10 (a) T2 image of a homogeneously appearing right frontal low-grade astrocytoma. (b) The tumour is not very conspicuous on diffusion-weighted images as diffusion and T2 effects cancel each other out (T2 masking). (c) Tumour becomes very conspicuous on the ADC map because of its relatively increased water diffusivity. Overall appearance on the ADC map is also homogeneous.

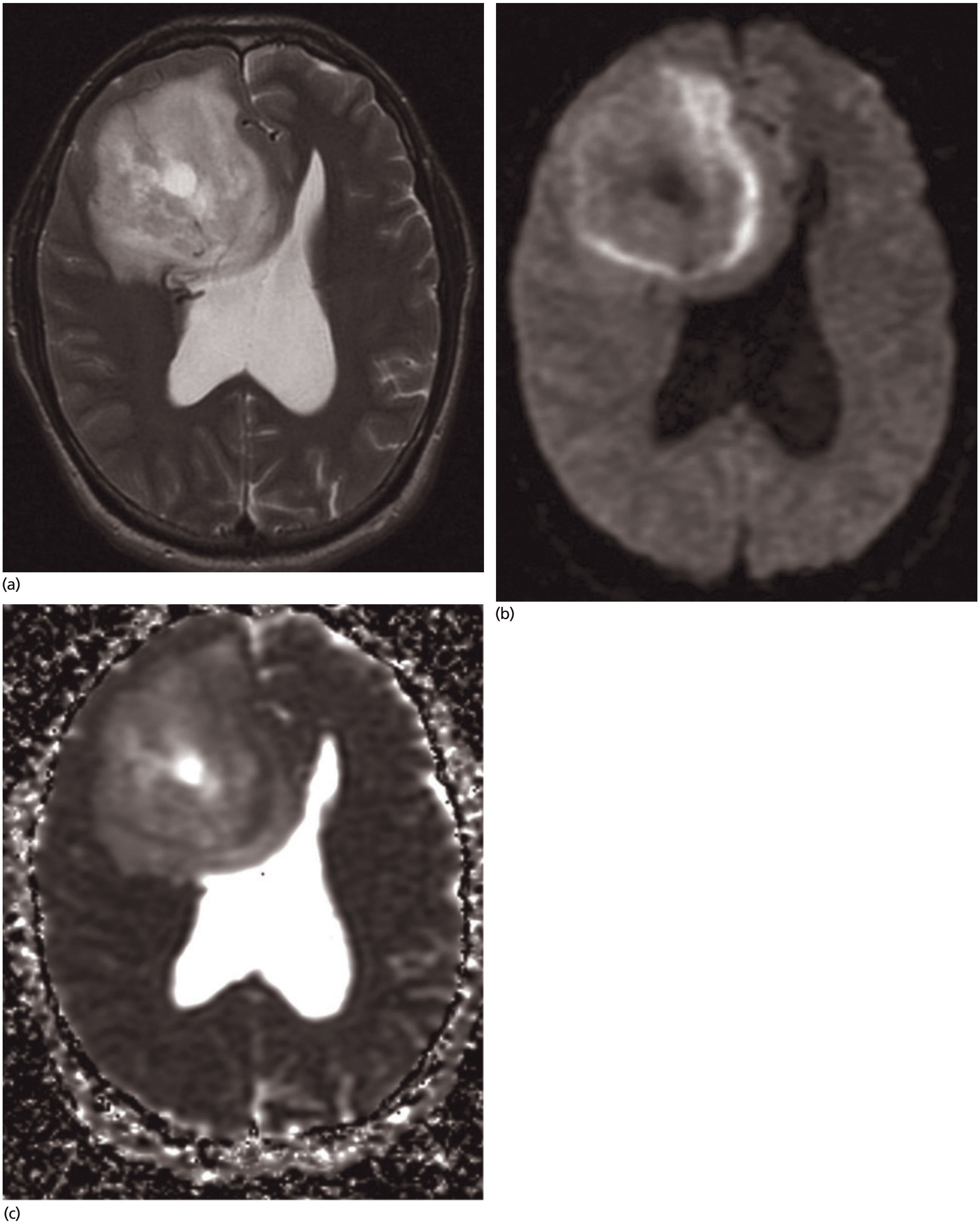


Figure 20.11 (a) T2 image of a high-grade anaplastic astrocytoma with a heterogeneous appearance. Note enlarged vessels at posterior aspect of mass. (b) Diffusion-weighted image shows a peripheral hyperintense rim, confirmed to be of restricted diffusion on the ADC map with a cystic necrotic centre. (c) ADC map confirms a centre of increased diffusivity (bright) and rim of decreased diffusivity (dark) as well as surrounding oedema (bright).

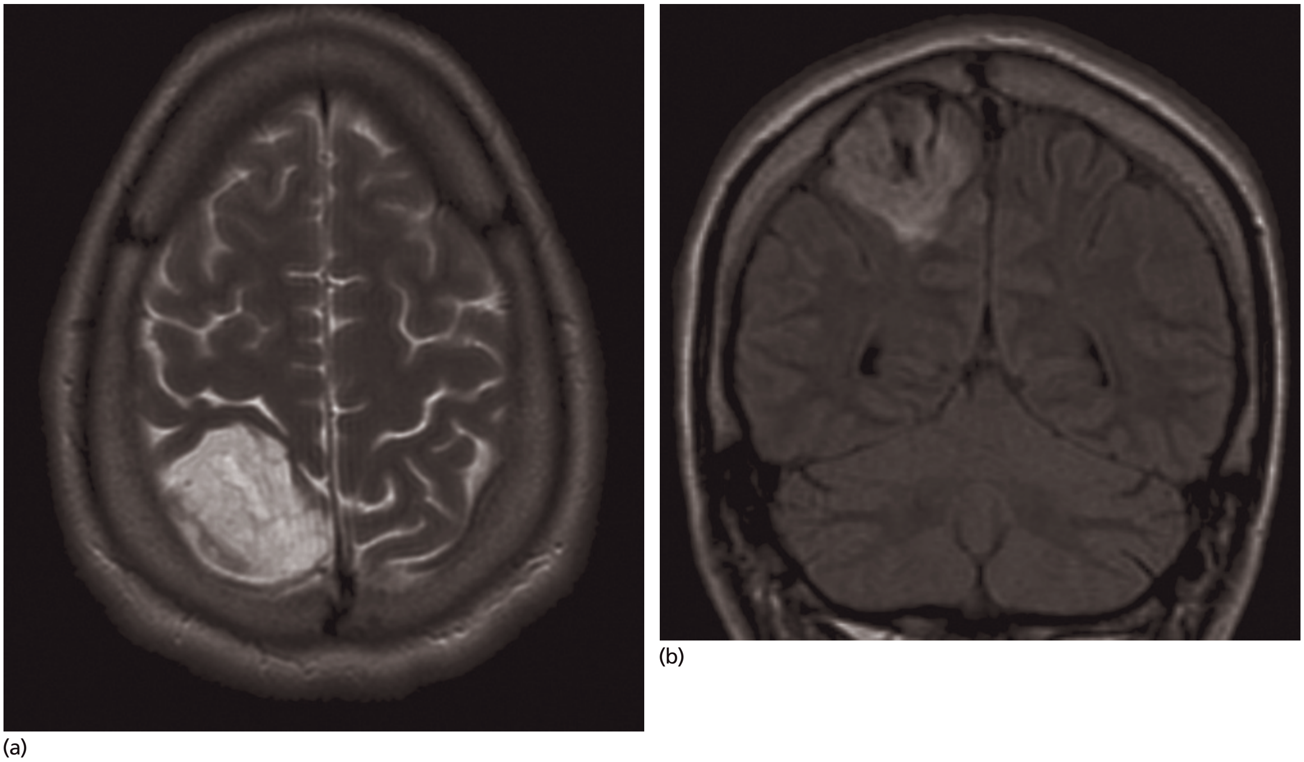


Figure 20.12 (a) T2 image of right parietal hyperintense mass that proved to be a dysembryoblastic neuroepithelial tumour (DNET). (b) Coronal FLAIR image shows cystic components within DNET with scalloping of inner table of the skull, indicating slow growth of this neoplasm.

Haemorrhage occurs in about 10% of metastases, resulting in high signal on T1 images and low signal on T2 images. Similar signal characteristics can also occur in non-haemorrhagic metastases from melanoma, because of the paramagnetic properties of melanin. Increasing the dose or relaxivity of gadolinium compounds can improve the sensitivity for detection of metastases on MRI.

DWI may help to predict the histology of brain metastases. Small cell lung cancer metastases and neuro-endocrine metastases have a lower ADC than adenocarcinoma metastases and appear bright on DWI (Figures 20.14 and 20.15). PWI and MRS of the peri-tumoural rather than intra-tumoural region help to differentiate a single metastasis from a high-grade glioma. DWI is helpful in distinguishing cystic metastases from cerebral abscesses. The latter contain more viscous fluid and pus; they show a more marked restriction of water diffusion than necrotic tumours.

Extra-axial tumours

Meningiomas

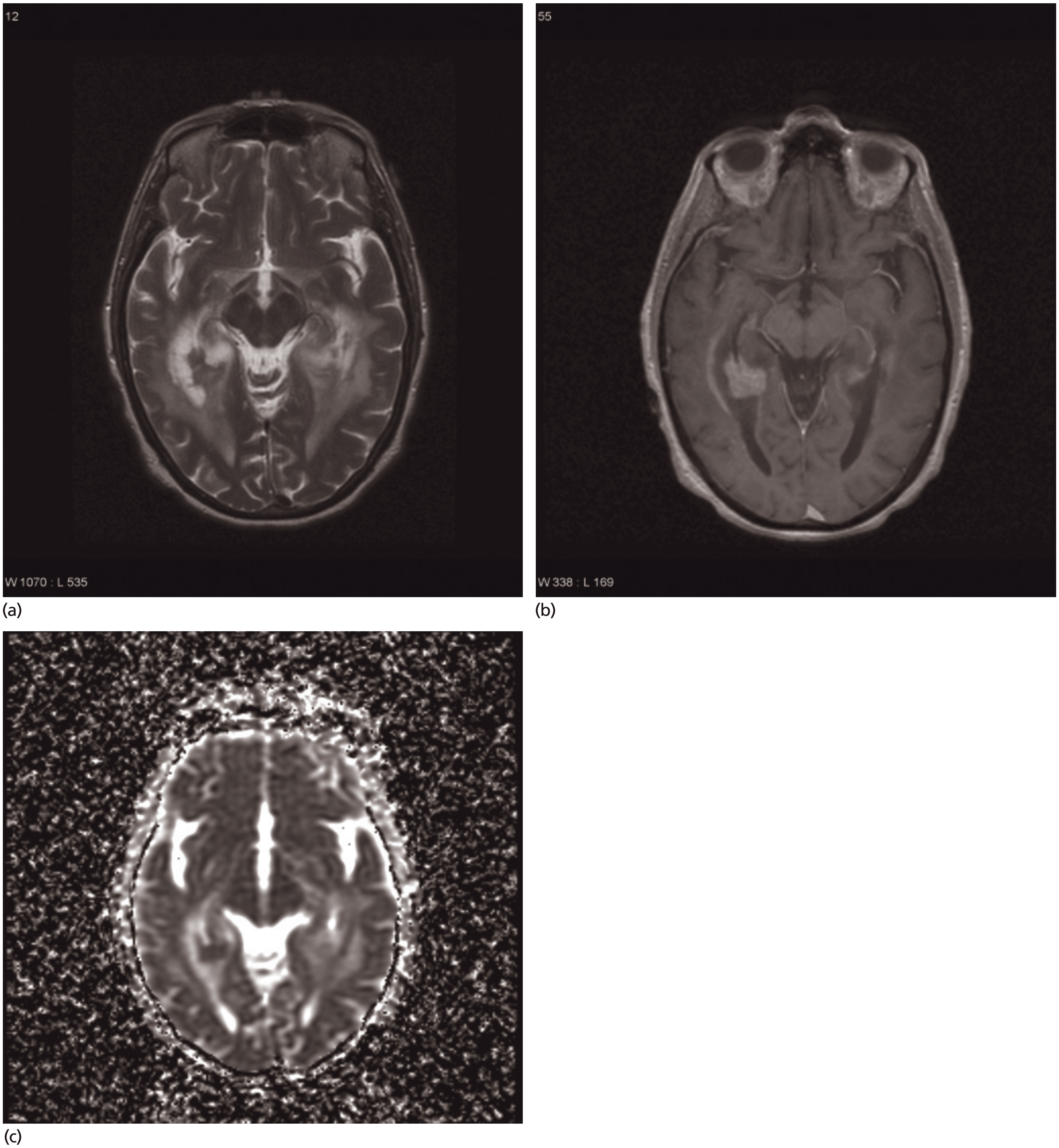
Meningiomas (WHO Grades I–III) can be spherical and well-circumscribed, craggy and irregular or flat, infiltrating en plaque lesions. They arise within the parasagittal area, convexities, sphenoid wing, tuberculum sellae, olfactory groove, tentorium and foramen magnum. Spinal meningiomas usually arise dorsally in the thoracic spine almost exclusively in women. On CT 60% of meningiomas are hyperdense without contrast and some 20% contain calcification. Hyperostosis, best seen on bone window settings indicates the site of the tumour attachment to the meninges. On MRI, meningiomas appear frequently isointense to cerebral cortex on both T1 and T2 images and may occasionally be difficult to detect without IV contrast. They can have capping cysts of CSF signal intensity. Associated vasogenic oedema is not infrequent and often disproportionate to tumour size.

Meningiomas enhance vividly and homogeneously. Linear enhancement can extend along the adjacent dura mater (Figure 20.1). This sign, known as the dural tail, was once thought to be pathognomonic for meningioma but can also be seen with other tumours such as schwannomas or even metastases.

DWI helps to distinguish between typical (WHO Grade I) and atypical (WHO Grade II) meningiomas; the latter having lower ADC values. MRS may show an alanine peak, characteristic for meningioma but seen in less than 50% of cases. PWI of meningiomas shows typically a markedly elevated rCBV, which can be of help in differentiating these benign tumours from dural metastases which tend to have a lower rCBV.

Epidermoid and dermoid tumours (WHO Grade I)

Intracranial dermoid cysts lie usually near the midline and contain all skin elements, including fat, which appears as very low density on CT and high signal intensity on MR T1 images.



(a)

(b)

(c)

Figure 20.13 (a) Axial T2 image in a patient with cerebral lymphoma: hypointense mass lesions and extensive temporal lobe peri-ventricular oedema. (b) Contrast-enhanced T1 image shows enhancing masses and irregular subependymal enhancement. (c) Enhancing lesions appear dark on ADC map, in keeping with a highly cellular neoplasm and typical of lymphoma. Surrounding oedema appears bright.

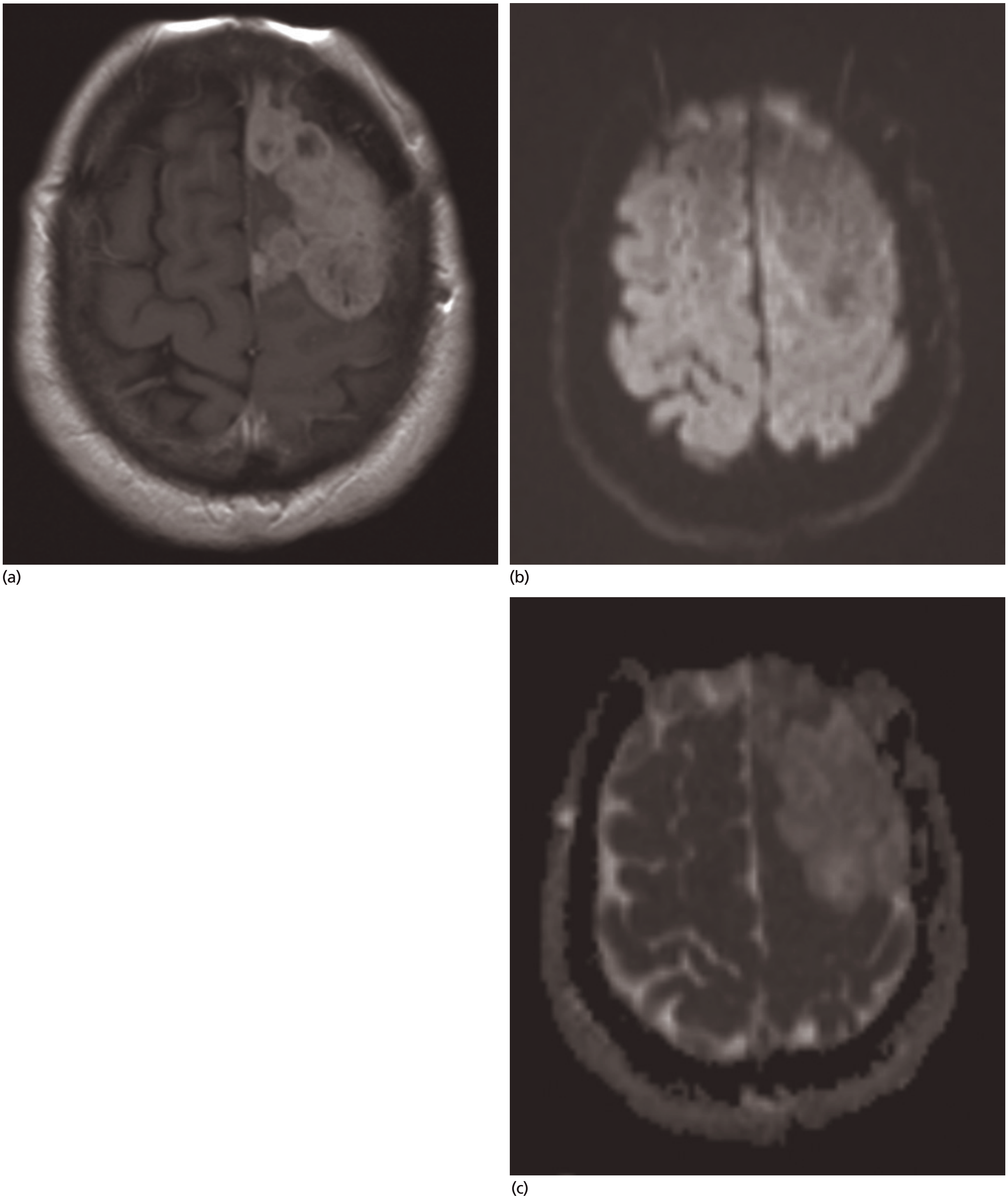


Figure 20.14 (a) Contrast-enhanced T1 image of a left frontal metastasis from a squamous cell bronchial carcinoma. (b) Diffusion-weighted image shows a relatively hypointense mass. (c) ADC map confirms increase water diffusivity within the tumour (bright), a feature of squamous cell carcinoma.

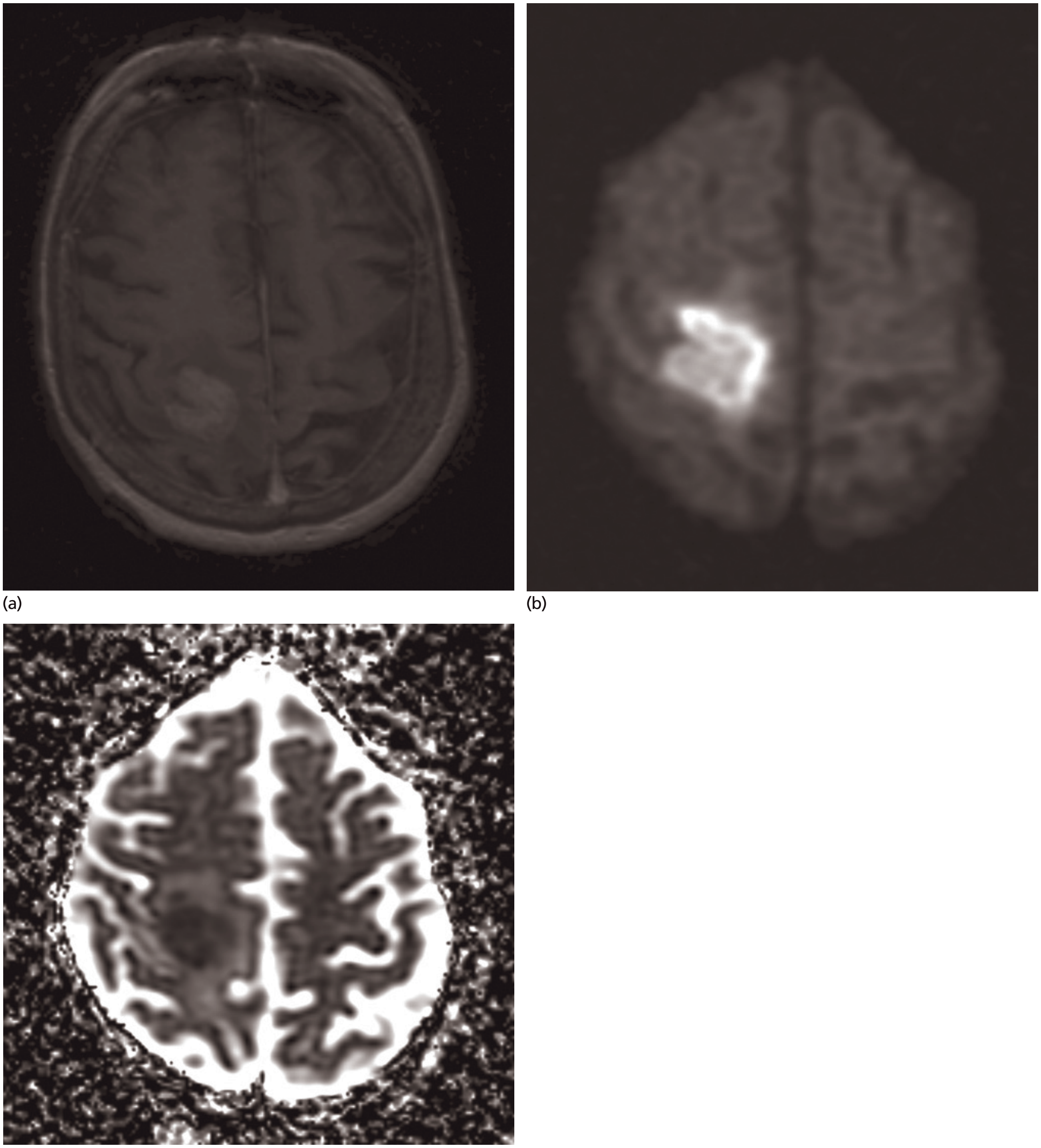
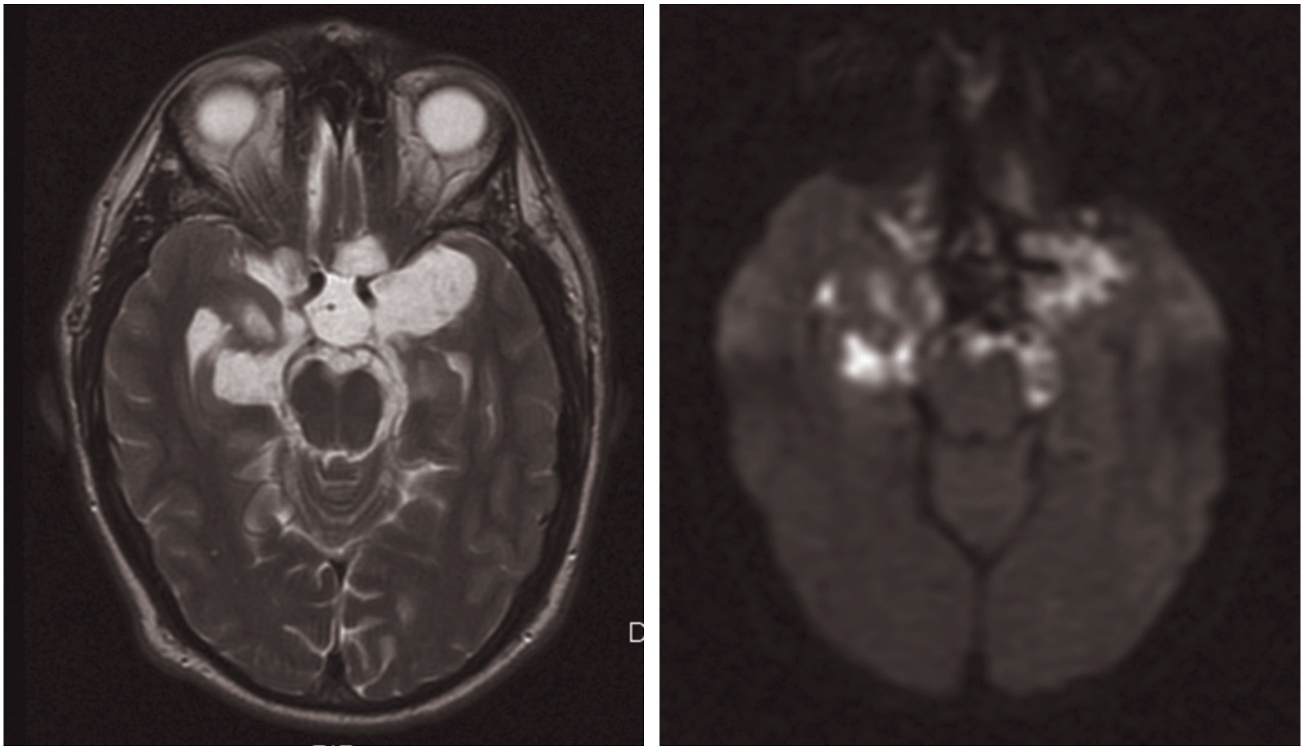


Figure 20.15 (a) Contrast-enhanced T1 image of a right parietal metastasis from a small cell lung carcinoma. (b) Mass appears markedly hyperintense on diffusion-weighted image. (c) ADC map confirms decreased water diffusivity within the tumour (dark), consistent with a highly cellular metastasis.



(a) (b)

Figure 20.16 (a) T2 image of an extensive epidermoid tumour spreading through the basal cisterns and invading the temporal lobes. (b) Diffusion-weighted image of the epidermoid tumour: characteristically bright and well delineated from surrounding CSF and brain parenchyma.

Epidermoid cysts, formerly known as pearly tumours, grow slowly over many years by accumulating desquamated epithelium. They conform to the contour of the subarachnoid space they occupy, sometimes invaginating into the brain parenchyma. On CT and standard T1 and T2 MRI, epidermoid cysts are non-enhancing lesions of signal intensity to cerebrospinal fluid (CSF), a reason why they can be confused with arachnoid cysts. DWI easily distinguishes epidermoid tumours from arachnoid cysts, as water diffusion is markedly restricted in the former but not in the latter (Figure 20.16).

Monitoring tumour growth and response to treatment

Change in tumour size has in the past been the most important imaging criterion for the evaluation of treatment response. Many treatment protocols for solid tumours recommend unidimensional or bi-dimensional measurements of tumour size. Volumetric (three-dimensional) tumour measurements are better predictors of patient survival than linear or two-dimensional tumour measurements. Volumetric contrast-enhanced T1 images are valuable in any serial imaging protocol that aims to assess tumour progression or treatment response.

Parameters detectable with physiological MRI have an increasing role in monitoring disease progression and early effects of treatment. This pertains particularly to measurements of rCBV and K^{trans}. The strength of these perfusion techniques lies in their ability to detect changes within internal tumour architecture in the absence of or prior to an overall change in tumour size.

Serial PWI of conservatively treated low-grade gliomas show an increase in rCBV 12 months before visible tumour enhancement, the conventional marker of tumour progression. PWI and permeability measurements have also been used to monitor antiangiogenic therapy. A significant fall in rCBV was observed in one study some 2 months after combination antiangiogenic and carboplatin therapy but not after carboplatin alone. Measurements of rCBV also correlate better with clinical status than conventional MRI. PWI has also demonstrated a significant reduction of rCBV in enhancing cerebral mass lesions treated with dexamethasone, an important fact to consider when comparing different treatment regimens.

Surgical treatment can be rendered more efficient with intra-operative MR brain imaging. The technique can be used to check for residual tumour following initial resection. This has been shown to increase the extent of complete tumour removal compared with neuro-navigation alone.

Imaging appearances of complications of treatment

Radiotherapy

The effect of radiation on the brain has a time-dependent course, with a distinction between acute, early-delayed and late-delayed

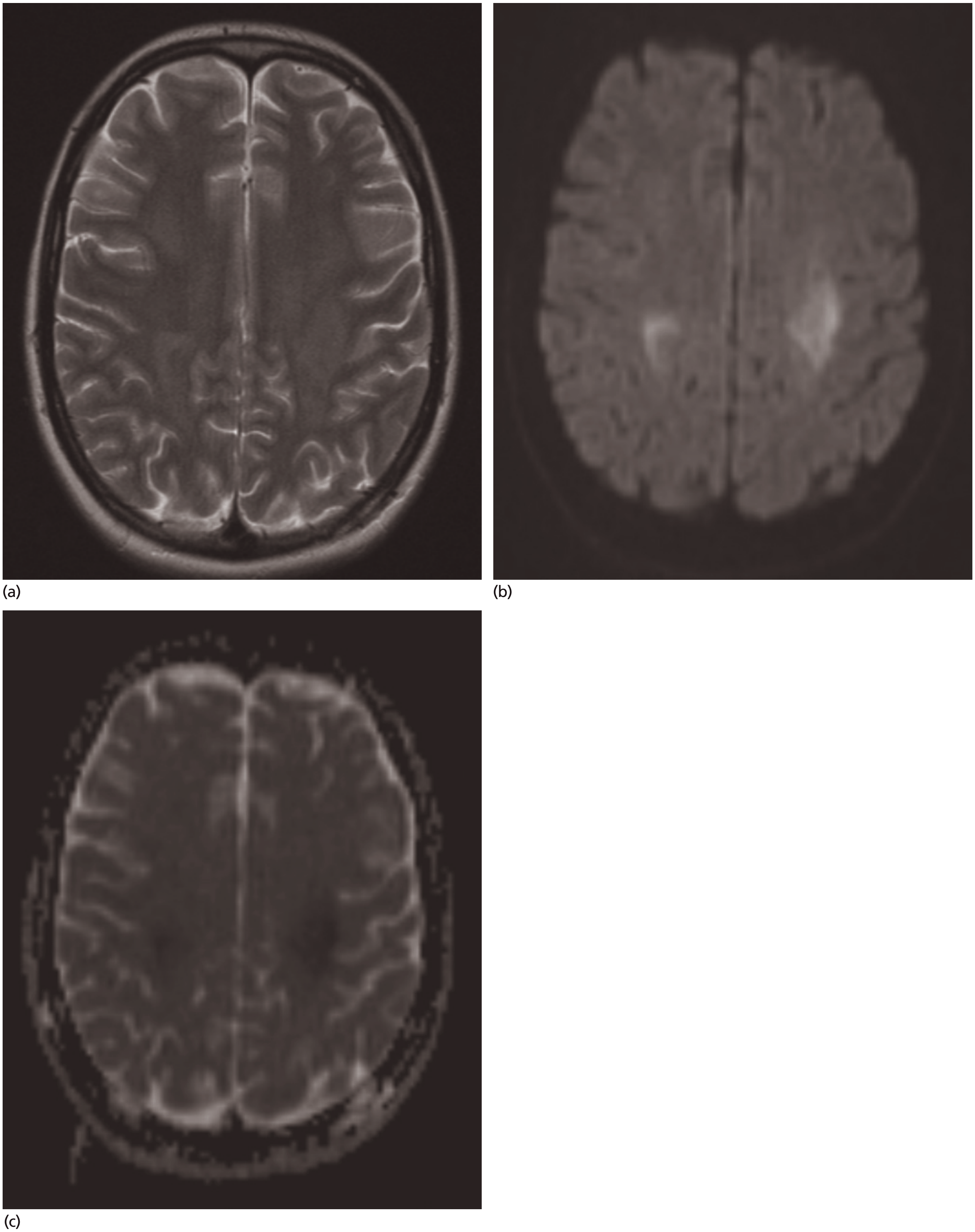


Figure 20.17 (a) T2 MR in a 6-week-old child following intrathecal methotrexate for acute lymphoblastic leukaemia (ALL) shows very subtle signal increase in parietal white matter. (b) Diffusion-weighted images show much more conspicuous increase of signal intensity in the posterior part of the centrum semiovale. (c) ADC map confirms restricted diffusion in the posterior white matter, a feature of methotrexate toxicity, potentially reversible.

radiation injury (Chapter 18). Severity depends on the total radiation dose, individual fraction size and volume of brain irradiated. Imaging is especially helpful in the diagnosis of late-delayed radiation-induced leucoencephalopathy and radiation necrosis.

Radiation-induced leucoencephalopathy

Radiation-induced leucoencephalopathy is a late-delayed demyelinating process that involves the peri-ventricular region and can extend into the juxtacortical region in more severe cases. On MRI it appears as non-enhancing, confluent, usually symmetrical areas of T2 hyperintensity, typically 6 months or more following radiotherapy.

Radiation necrosis

Radiation necrosis is also a late-delayed complication of radiotherapy and radiosurgery, which can appear similar to an enhancing mass lesion and thus be difficult to distinguish from recurrent tumour on conventional imaging. PWI and DWI may help to distinguish between radiation necrosis and tumour recurrence (Plate 20.10). In radiation necrosis the enhancing lesion has a low rCBV, whereas this tends to be high in tumour recurrence as a consequence of increased new vessel formation. ADC measurements of the enhancing components in recurrent tumour are significantly lower than in radiation necrosis, mirroring the higher cellular density in recurrent neoplasm.

Other complications

Optic neuropathy is most commonly seen following radiotherapy of sellar and parasellar lesions and is a late-delayed complication of radiotherapy, with T2 hyperintense signal change typically in the intracranial portion of the optic nerve.

Meningiomas are the most commonly encountered radiation-induced tumours, with typical latency periods over 10 years. Gliomas and schwannomas are also seen, developing many years after radiotherapy. Radiation-induced cavernomas are more common than previously assumed; their detection rate is significantly increased with the use of haemorrhage-sensitive gradient echo MR sequences.

Chemotherapy

A large number of chemotherapeutic agents are neurotoxic. Combining chemotherapy and radiotherapy can result in additive and synergistic effects. The most frequent imaging findings are posterior leucoencephalopathy (Chapters 18 and 19), with bilateral, typically symmetrical white matter lesions of low density on CT but T2-hyperintense on MRI. These are most commonly seen following methotrexate, even when given alone. In the acute stage abnormalities may be undetectable on T2 images and only become apparent on DWI and ADC maps (Figure 20.17).

Management in a multi-disciplinary setting

The management of benign or malignant brain tumours has long been known to require the disciplines of clinical neurology, neuroradiology, neuropathology, neurosurgery, radiotherapy, oncology, specialist nursing, general practice and palliative care. Within the last decade a further dimension has been clearly defined – an approach that unites these disciplines into therapy that is focused on improving the quality of life, with greater involvement of both patient and carers in the therapeutic process. There are decisions to be made about diagnoses of the utmost gravity. One significant advance, sometimes painful to all, is to discuss frankly the probable prognosis, the limited choice of therapy available and the uncertainty of outlook in an individual case.

Improving outcomes and quality of life

The impact of a diagnosis of a brain tumour upon a person's life is profound and multi-faceted. Patients experience both physical effects of the tumour and side effects of treatment. They and their carers have to cope with the emotional impact and psychological effects of living with a life-threatening illness. The diagnosis is likely to be the major life event to date and to colour every aspect of the remaining months or years. Cognitive deficits, of memory, speech and language, behavioural changes and physical decline combine to produce a formidable burden. When cognitive problems are prominent, recovery from or preservation of cognitive function has been shown to be, in the main, more important to patients than loss of physical function. To plan treatment and gain consent from patients with cognitive impairment is difficult. Progressive cognitive decline presents a continuing challenge for patients, carers and all involved in providing care.

Multi-disciplinary working is essential to improving outcomes for these patients, providing access to specialist services though collaboration between neurosurgery, radiotherapy, oncology and community teams. The ideal model of service provision promotes a unified care pathway, incorporating physical, psychological, supportive and palliative care for patients and carers. There is no doubt that quality of life can be enhanced by skilled key workers, good communication with patients and carers, access to high-quality information, specialist rehabilitation, supportive and palliative care. Above all, patient and carer need a central point of contact and a scheme for action in emergencies and for intercurrent problems. The development of charitable support networks has helped towards providing non-hospital based support for patients, families and carers.

It is often the neuro-oncology clinical nurse specialist who has a primary role in providing information, advice and support to patients and carers at the time of diagnosis, during treatment and disease progression and facilitates continuity of care across the disciplines involved.

Surgical management of brain and spinal tumours

Surgery remains the mainstay of treatment for brain tumours, ranging from stereotactic biopsy to open craniotomy and resection of tumour. The overall goals of surgery are to obtain a histological diagnosis, relieve mass effect and improve focal neurological deficit, and the ultimate goal to allow for cure of the tumour. More often than not however, surgery only offers theoretical improvement in response to adjuvant therapy. Over the last decade neurosurgery, in particular for brain tumours, has benefited significantly from technological advances. Neuro-navigation guided biopsy and surgical resection, awake craniotomies using neurophysiological monitoring together with cortical mapping, microsurgical techniques combined with minimally invasive neuro-endoscopy and intra-operative real-time neuroimaging have made a significant impact on the outcome of surgery and patient morbidity and mortality.

General principles

The neurosurgical techniques used for brain tumours include image-directed biopsy, either by frame-based, stereotactic methods or by frameless methods using neuro-navigation techniques, with craniotomy for partial or gross total tumour resection. In addition, specific subspecialty tumour surgery include skull base, pituitary and sellar tumours, which have all benefited from use of neuro-endoscopy and allowed for extensive operative techniques to be converted to minimally invasive surgery, with significantly lower morbidity and mortality.

With all tumours, total macroscopic excision is the surgical aim, but this is only realistic in a limited proportion, given the high eloquence of brain structure. Tumours frequently either infiltrate eloquent brain anatomy or are intimately involved with very sensitive anatomical structures such as the optic nerve, cavernous sinus or the petro-clival region. Complete resection is commonly possible with extra-axial tumours, in particular meningiomas or sometimes metastatic tumours, but rarely possible with intrinsic tumours. The most difficult of this category are the low-grade gliomas, given the extensive invasive nature often into eloquent cortical structures. Tumours of the middle and posterior skull base require highly specialized surgical avenues such as trans-oral, maxillotomy, retro- or trans-labrynthine routes to make access possible, while avoiding injury to critical neural structures, e.g. specific cranial nerves and sensitive vascular anatomy.

Surgical instrumentation and methods

Stereotactic frames

A large variety of CT and MRI compatible stereotactic frames are available which can be rigidly applied to the patient's head for surgical biopsy by pins affixed to the outer table of the skull. Frame-based stereotactic biopsy renders an accuracy of about 1–2 mm, with the most accuracy achieved for deep-seated lesions versus more superficial lesions. Frame-based stereotactic biopsy can be used to obtain a histopathological diagnosis of all regions of the brain, including deep structures such as the thalamus, basal ganglia or brainstem. The complication rate associated with stereotactic biopsy is low; the most major complications are a consequence of bleeding. Overall risks include a <1% risk of mortality, 1–5% risk of serious morbidity and 2–3% risk of minor morbidity. The method generally achieves a definite histological diagnosis in 95% of cases; the diagnosis is significantly different from the pre-operative neuroradiological diagnosis in 5–10%.

Neuro-navigation and frameless stereotaxy

In the past decade stereotactic biopsy techniques have gradually been replaced by frameless stereotaxy, a technique that employs neuro-navigation technology. Neuro-navigation involves computer-assisted technologies to guide or navigate the neurosurgical approach. Using mathematical coordinates to identify structures within a defined space, e.g. the skull, neuro-navigation allows highly accurate localization of structures. This is achieved by real-time fusion of pre-operative imaging of the patient's brain, using either CT or MRI, which includes fiducial markers on the patient's scalp to define a coordinate system of the desired space. The patient can be registered to the neuro-navigation system pre-operatively; this provides the surgeon with the ability to relate the position of a real surgical instrument within the surgeon's hand or microscope's focal point to the location of the imaged pathology, updated in real time. The neurosurgeon is able to create a three-dimensional model that can be manipulated to examine and explore the location of the tumour in relation to normal anatomical structures, in addition to examine alternative surgical approaches prior to the definitive surgery. Virtual images are displayed on a monitor visible to the surgeon, who can interact with this image with a sterile pointer during the operation. Regions of exposed brain can be touched by the pointer and the position in space correlated with the position of the tumour shown on the peri-operative scan. This method is slightly less spatially accurate than frame-based stereotaxy, within the region of 3 mm variation, particularly as there is inevitably some brain shift when the skull and dura are opened; overall accuracy is within 10 mm.

Neuro-navigation can be used both for biopsy and gross tumour resection. It has been shown to be efficient for biopsy, except for deep small targets in the brain. For tumour resection, its main advantage is being able to tailor and fashion the craniotomy and surgical approach for individual tumours, providing increased confidence, and giving a rough guide to determine extent of tumour resection intra-operatively. Operative mortality is about 2%, with serious morbidity of about 5–6% and minor morbidity of a further 5–6%. The limitations of neuro-navigation are that it is based on previously acquired imaging datasets; the system does not allow for correction of brain shift, a result of dura being opened, pressure changes occurring within intracranial space, CSF leaking out and brain oedema. In an attempt to eliminate the short-comings of neuro-navigation systems, real-time imaging modalities have evolved, such as intra-operative diagnostic ultrasound and intra-operative MRI.

Intra-operative diagnostic ultrasound

Ultrasound has been used in neurosurgery for over two decades. Precise localization of lesions in the brain is a challenge, and methods to minimize and eliminate exploration and dissection in the brain parenchyma are constantly being sought. Pre-operative CT and MRI images provide ideal road-maps for surgical planning; however, they are limited in their ability to determine the precise location of lesions intra-operatively, in particular deep lesions beneath the cortical surface. Real-time images obtained from intra-operative ultrasound provide dynamic information on localization, in depth, orientation, mass effect and presence of cystic components; ultrasound can facilitate cyst drainage and alleviate pressure prior to tumour excision. Ultrasound can also be used to confirm extent of tumour resection.

Intra-operative MRI

Interventional MRI (iMRI) is a real-time intra-operative adjunct for guiding surgery without ionizing radiation, providing exquisitely detailed imaging compared to CT. Surgical navigation can be repeatedly updated by intra-operative and dynamic images of the brain and lesion while surgery is proceeding, and account for the changes that occur as a result of CSF leakage, oedema and hemorrhage. The main advantage of iMRI is that it allows the surgeon to identify the extent of residual tumour that can be resected. The use of physiological iMRI to understand more clearly the pathology of brain tumours is promising. However, iMRI suites are available in very limited neurosurgical centres. Its real value as an operative adjunct has yet to be established.

Neuro-endoscopy

Technological advances in neuro-endoscopy, improved optics, video and camera systems has made neuro-endsocopy and minimally invasive neurosurgery a routine technique not only for pituitary but also for skull base tumours. Large and extensive exposures are required for upper cervical spine and clivus lesions, through trans-oral or ‘open door’ maxillotomy approaches and resection of the odontoid which have in the past been associated with significant morbidity. These areas can now be approached using endoscopic trans-nasal approaches. Endoscopic approach possesses some inherent advantages, including decreased exposure to oral flora and excellent visualization, while at the same time minimizing prolonged retraction. Most centres that incorporate neuro-endoscopy and minimally invasive surgery do so in close collaboration with their head and neck, and ENT colleagues.

Surgical techniques and microsurgery

Introduction of microsurgical techniques revolutionized neurosurgery in the early 1950s. Out of frustration with the extent of visualization of intracranial pathology, neurosurgeons introduced the operating microscope, which provides not only magnification but also illumination. The wide range of microsurgical instruments used today were designed by pioneers of microsurgery – Yasargil, Rhoton, Hardy, and many others.

An important adjunct for tumour resection is the ultrasonic aspirator. High-frequency vibration fragments and cavitates tissue coupled to suction which aspirates the morsalized fragments. The ultrasonic aspirator is capable of removing a wide range of tissue and demonstrates differential susceptibility to tissue type based on water content, more readily allowing resection of brain parenchyma and mucous membranes with high fat and water content, versus tissue with higher elastin content such as blood vessels and nerves. Ultrasonic aspirators provide the advantage of causing limited injury to surrounding tissue. Removal of various tumour types has been revolutionized using ultrasonic aspirators; the technique can be used to remove entire tumour, debulk the central core and facilitate microdissection from delicate structures such as the optic nerve or major vessels.

Radiosurgery

Radiosurgery harnesses image-directed surgical planning with focused high-dose radiation delivery to the selected target. In this sense it is more akin to surgical ablation than to radiotherapy. The technique is used increasingly for cerebral metastases and for relatively inaccessible skull base tumours such as chordomas, meningiomas and vestibular schwannomas.

Surgical considerations for specific tumours

High-grade gliomas

The most common primary brain tumour is the high-grade cerebral glioma (WHO Grade III or IV). Histological diagnosis is mandatory, except in situations where the condition of the patient is so poor that no treatment is indicated. Diagnosis can be obtained either by biopsy alone or on tissue obtained during craniotomy and gross tumour resection. Relative indications for resection and debulking of a tumour are for symptomatic relief of raised intracranial pressure or focal neurological deficits, created as a result of tumour mass effect and compressing eloquent cortical structures but not where tumour has invaded eloquent structures directly. Invasion of eloquent brain areas is the limiting factor in achieving complete gross tumour resection.

Malignant gliomas infiltrate surrounding normal brain and surgical cure is therefore not possible, even with very extensive resections. The principle of oncological cytoreduction enhancing the efficacy of adjuvant therapies is invoked in support of macroscopic complete resections and is therefore offered to patients at the better end of the prognostic spectrum, i.e. younger age and higher performance status. However, the value of extensive surgical resection for high-grade gliomas is a long-standing controversy in neuro-oncology. Definitive studies have not been able to tackle this, as high-grade tumours are microscopically invasive; hence intra-operative margins of tumour cannot be identified, the definition of tumour resection is often non-quantitative and the risk of neurological deficits with extensive resection limits the volume of tumour resected. In general, it is accepted that >80% tumour resection provides oncological advantage by providing cytoreduction and improving response to adjuvant chemo- and radiation therapy. A few centres suggest that resection of >98% is an independent variable associated with longer survival, with an approximate 3-month survival advantage compared to patients with 80% resection. In a small proportion of patients with recurrent disease, a second resection (11%) or a third resection (4%) is performed, again in younger patients with high performance status who have responded well to first line treatment.

Low-grade gliomas

Low-grade (WHO Grade II) glioma typically presents with epilepsy in young adults; investigation with CT or MRI reveals a low-density or high-signal non-enhancing lesion. The timing of neurosurgical intervention, either in the form of image-directed biopsy or tumour resection, depends on many factors. However, with technical advances in pre-operative structural and functional imaging, there is a trend towards more extensive tumour resection, particularly as research has shown that all low-grade gliomas grow steadily and that the vast majority transform into high-grade gliomas at some point in their natural history. Recent data from a single centre suggests that larger, safer resections can be carried out by direct intra-operative electrical stimulation and may be associated with an improvement in long-term prognosis. However, even in the hands of a dedicated low-grade glioma neurosurgeon, only 25% of tumours are completely resectable.

Awake craniotomy with cortical mapping provides the opportunity to maximize tumour resection, while minimizing neurological deficits and overall morbidity to the patient compared to standard craniotomy performed under general anesthesia. In the case of low-grade gliomas, in particular for tumours that are located primarily subcortically with minimal to no abnormality evident on surface cortical structures, identification of eloquent cortex is of paramount importance, hence use of awake craniotomy is advocated, largely in cases where on pre-operative high-resolution MRI tumour infiltrates are found within or adjacent to anatomical eloquent cortical landmarks. A battery of diagnostic tests can be performed pre-operatively to aid in characterizing the relationship of tumour to eloquent cortex. MRI is helpful in defining the anatomical sulcal and gyral patterns correlating tumour location to motor, sensory and speech cortex. In addition, MRA may be helpful in defining critical vascular structures surrounding and often involving tumour boundaries. Functional MRI (fMRI) provides more accurate localization of motor and sensory cortex in addition to expressive speech centres, with receptive speech or comprehension being less accurately identified on fMRI. DTI can identify white matter tracts adjacent to or infiltrated by tumour, which can help planning surgery pre-operatively. Neuropsychological testing is used to establish dominance for speech and memory, in addition whether any functional compromise has occurred from mass effect or infiltration by tumour into the mesial temporal structures.

Information gathered from pre-operative diagnostic tests is combined with data obtained during intra-operative neurophysiological testing to identify areas of critical function, the area of pathology and safe corridors of entry into the cortex. Therefore, the surgeon is given greater confidence, because great variability exists in the morphology of cortical structures and their landmarks, and recognition of sulcal and gyral patterns intra-operatively is rarely straightforward. During cortical stimulation, the patient is asked to perform tasks testing motor and sensory function. Language testing is more accurately carried out using specific language paradigms and visual cards than counting or naming of objects, days or the alphabet. Therefore, a dedicated team is required in order to carry out complex awake craniotomies together with cortical mapping. If the patient is under general anaesthesia, although the extent of cortical mapping will not be to the same accuracy as in awake craniotomy, somatosensory evoked potentials (SSEPs) can be used to identify motor and/or sensory cortex. Surgeon comfort, patient preference, availability of pre-operative and intra-operative tests along with a dedicated neuro-anaesthesia team are key factors for performing awake craniotomies; few centres that offer neurosurgery have such capabilities. Management of low-grade gliomas is best carried out in centres that support awake craniotomies and cortical mapping.

Meningiomas

Completeness of surgical removal of tumour is the single most important prognostic factor for patients with meningiomas. Various characteristics of meningiomas have been used to predict tumour recurrence, such as anatomical location, extent of tumour resection and histopathological features, with the single most important prognostic factor being the completeness of surgical resection. Simpson introduced a classification system that can predict recurrence rates based on extent of tumour resection, (Table 20.2). This classification system has been modified to include extent of microscopic resection; however, the Simpson classification remains the most widely used system. Tumour histology is also an important factor in predicting recurrence, if the tumour exhibits anaplastic and malignant features (WHO Grade

Table 20.2 Prediction of recurrence rates for meningiomas.

Recurrence	Grade	Description
10%	I	Macroscopically complete removal, excision of dural attachment
20%	II	Macroscopically complete removal, coagulation of dural attachment
30%	III	Macroscopically complete removal, without resection or coagulation of dural attachment
40%	IV	Partial removal
	V	Decompression/biopsy

II–III), the rate of recurrence is significantly higher, with 3% recurrence predicted for benign meningiomas, versus 40% for atypical and 80% for malignant meningiomas over a 5-year period.

The introduction of new surgical approaches has improved operability of meningiomas at some previously relatively inaccessible sites. Radiosurgery and focused fractionated radiotherapy has also provided improved control of residual and/or recurrent meningioma. Pre-operative embolization in very vascular meningiomas is sometimes advocated to reduce peri-operative blood loss.

Brain metastases

Patients with brain metastases are an increasing population, as improvements in systemic chemotherapy have led to more patients surviving and developing brain metastases. As a result treatment options and paradigms for patients with brain metastases are evolving. Available options for brain metastases currently include focal treatment, in the form of brain surgery and radiosurgery, and non-focal treatment using the standard and previously accepted treatments, whole-brain radiotherapy and chemotherapy. Novel treatment paradigms should combine these various treatment modalities in order to provide the most comprehensive and tailored therapeutic option for individual patients. General indications for surgery on brain metastases include *de novo* presentation in the brain, without a known primary tumour being diagnosed; in this case resection of the brain lesion will provide diagnosis in addition to excision. Surgery should also be considered if a metastatic tumour has associated oedema, mass effect and focal deficits or seizures that are not controlled on antiepileptic therapy; tumours larger than 3 cm in diameter should be considered, because this size excludes consideration of radiosurgery. Surgical resection of solitary metastases followed by whole brain radiotherapy (WBRT) results in a longer median survival (10 months versus 3.75 months) and extended functional independence compared to WBRT alone; this is recommended when the general condition of the patient is satisfactory and when the underlying primary disease is stable. Stereotactic radiosurgery (SRS) with either a cobalt source (gamma knife) or linear accelerator (LINAC based) may be used as an alternative to surgery, particularly for metastases in eloquent regions of the brain, although no head-to-head comparison with surgery has been carried out. In a large randomized Radiation Therapy Oncology Group (RTOG) trial the value of adding a radiosurgery boost to WBRT has been demonstrated by improving overall survival and performance status, together with the benefits of tapering off steroids faster. The same RTOG study showed that for patients with multiple metastases, radiosurgery boost is beneficial if the patient has stable systemic disease and good performance status. There are no studies demonstrating benefits of surgery for multiple metastases; common practice does not advocate surgery for multiple lesions, but only considers surgical resection for the lesion that generates mass effect, oedema and focal neurological deficits, in order to help improve quality of life and decrease need for steroids.

Primary spinal tumours

Primary tumours of the spinal cord are relatively rare and are chiefly astrocytomas or ependymomas, usually low-grade, affecting commonly the cervical cord or, in the case of ependymomas, the conus. Other, less rare, primary spinal tumours are meningiomas arising from the dura, schwannomas arising from the spinal nerve roots and lipomas, either intramedullary or extramedullary.

The symptoms and signs at presentation are a combination of the effects of nerve root involvement at the level of the tumour, e.g. girdle pain, and the effects of long tract involvement at that level, e.g. paraparesis or tetraparesis. MRI is usually diagnostic.

Surgical treatment is indicated for extramedullary tumours via laminectomy at the appropriate level(s). Occasionally, more extensive approaches are required, e.g. with dumb-bell schwannomas, where thoracotomy or abdominal surgery may be required.

In the case of intramedullary astrocytoma, it is sometimes possible to enter the spinal cord posteriorly in the midline, between the posterior columns, or alternatively through the dorsal root zone. Tumours associated with a cyst can occasionally be dissected free from the normal structures with little morbidity, with an apparently total macroscopic removal. In the case of ependymoma, it is frequently possible to obtain a macroscopic total removal of the tumour. However, with this type of tumour there may be local and more distant seeding of tumours through the CSF pathways, requiring adjuvant treatment.

With spinal meningiomas, excision is usually curative and recurrence is uncommon, even when it has not been feasible to excise the dura widely. Similarly, most but not all schwannomas affecting spinal nerve roots can be cured by total excision. However, in some cases these tumours may have an aggressive course and not be surgically curable.

Metastatic spinal tumours

The spine is a common site for metastatic disease, commonly with bony involvement, but sometimes with extradural deposits and, rarely, with intramedullary spread. These tumours usually spread haematogenously into the vertebral bodies and cause epidural spinal cord compression. Typically, the clinical history is much shorter than with primary spinal tumours. Thus, patients may present as an emergency, with rapidly progressing paraparesis and urinary incontinence and/or retention. Referral may be delayed when there is no previous history of cancer, unless the true nature of the problem is identified. Oncologists are well aware of syndromes caused by spinal metastases, and in patients with a previous known history of malignancy, the diagnosis tends to be made promptly.

Speed of diagnosis followed by urgent imaging is of the essence in preventing or minimizing permanent neurological deficit. Where there has been a short clinical history and the patient has a severe paraparesis with sphincter function lost for more than 12 hours, the results of surgical decompression are poor. A recent randomized trial of surgery followed by radiotherapy against radiotherapy alone for metastatic spinal cord compression showed that significantly more patients in the surgery group were able to walk after treatment and retained the ability to walk significantly longer than in the radiotherapy group. The benefits of this trial cannot be applied to patients with multiple metastases and in this group urgent radiotherapy is usually offered, particularly where the tumour is likely to be radio-sensitive and the patient is deemed sufficiently well to survive for a number of months.

Patients with more rapidly advancing neurological deficits and with severe cord compression by tumour, as well as spinal disease, generally need urgent surgery if stabilization of their deficits is to be achieved. There has been a clear trend towards adjusting the surgical approach to the exact site of the metastatic tumour in order to obtain maximum decompression, coupled with fixation to stabilize the diseased spine. Major anterior or lateral approaches are suitable for anteriorly or laterally placed spinal metastases, but these often require a neurosurgeon to have assistance from a thoracic or abdominal surgeon. Single or multiple level corpectomy of the vertebral body with subsequent repair by bone cement, titanium-based cages or bone graft and concomitant posterior spinal fixation with metal instrumentation are performed more frequently than in the past. Posterior decompression should not be performed for anteriorly placed tumours as the resulting laminectomy can lead to spinal instability and rapid neurological deterioration when the patient is mobilised.

Radiotherapy and chemotherapy for common CNS tumours

The benefits of surgical treatment for the majority of intrinsic malignant tumours are limited by their aggressive biological behaviour together with considerations surrounding neurological deficits following removal of tumour tissue from infiltrated normal brain or spinal cord. Many CNS tumours, even benign WHO Grade I meningiomas, may recur many years after removal particularly if initial resection is incomplete. For these reasons, radiotherapy and chemotherapy play an important part of the overall management of primary intracranial and spinal tumours.

Brain radiotherapy: planning

Radiotherapy planning based on CT and MRI is now the standard approach to glioma treatment. CT-based planning allows accurate tumour dose localization and relative sparing of normal brain. The patient is immobilized in a plastic mask. CT slices (0.5–1 cm) are obtained in the treatment position. MRI data from diagnostic studies are then fused with CT data, to define the precise volumes to be treated to high dose. The patient is usually treated in the supine position unless the tumour volume lies very posteriorly. This position is most easily reproducible and the most comfortable. The field arrangement is chosen to encompass the tumour volume with maximal sparing of surrounding brain, usually utilizing 2–3 fixed fields. Using modern conformal radiotherapy techniques, scanning and planning software permits reconstruction of three-dimensional anatomy. The tumour and target volumes are visualized from the plane of the incoming radiation beams. Using these data the radiotherapist can then design shielding that conforms closely to the tumour volume, giving a steep dose gradient between tumour and normal brain. Total radiation doses given are usually in the range 45–60 Gy, with typical daily fractions of 2 Gy.

Stereotactic brain radiotherapy

A refinement of conventional brain radiotherapy is to combine conformal planning with stereotactic techniques for both immobilization and tumour localization. This enables a further reduction in the treatment volume because of increased accuracy of tumour localization; relocation error is often reduced to below 1 mm. Relocatable stereotactic frames permit the dose to be given in a conventionally fractionated regime. Currently, these techniques are being explored in the treatment of gliomas, particularly in the paediatric population and for treatment of recurrent disease. Unfortunately, with gliomas, because the size of the treated volume is influenced most by the large clinical target volume necessary to include likely tumour infiltration, these techniques do not usually reduce the irradiated volumes by significant amounts.

A further development is Intensity Modulated Radiotherapy (IMRT). This enables the radiation dose to be modified throughout the treatment volume. This permits treatment of concave volumes, sparing organs at risk lying within concavities such as the pituitary.

Spinal radiotherapy: planning

Developments in radiotherapy planning technology have improved accurate delineation of spinal tumour masses using MRI data superimposed on CT scans in the treatment position. In most cases, MRI will be used to define the target lesion and fields designed to encompass this volume with 3–5 cm margins. Attention should be paid to anatomical influences on tumour spread, e.g. when treating disease in the conus medullaris the anatomical boundary to spread is at S3. Treating below this level will only add toxicity. In most cases, treatment fields do not need to extend further laterally than the lateral processes of the vertebral bodies, i.e. some 2 cm lateral to the border of the vertebral body. Patient positioning and immobilization for treatment are important to prevent dose inaccuracies or inhomogeneity. Radiotherapy doses for young female patients need to be reduced as far as possible. Planning systems that use three-dimensional imaging of the target conformal shielding can be a great advantage in these situations. It is generally safe to irradiate limited volumes of spinal cord to doses of 50–55 Gy. Animal data suggest a relatively small effect of volume once treatment lengths of 8 mm are exceeded. Estimates of the total dose to give 5% toxicity rate at 5 years (TD 5/5) using 2 Gy fractions are between 57 and 61 Gy: previously damaged spinal cord probably has a lower radiation tolerance.

Brain and spinal cord irradiation: toxicity issues

Radiotherapy-induced neurotoxicity is seen commonly following treatment of even relatively benign CNS tumours both in children and adults. Radiation damage to the brain and spinal cord is categorized according to the time at which the clinical features develop. Acute, early-delayed and late-delayed radiation effects must be considered. As a general rule, acute and early-delayed toxicity are reversible and improve spontaneously and/or with steroids. Late-delayed toxicity is irreversible.

Brain irradiation

Acute toxicity

Common acute effects include alopecia, scalp erythema, fatigue, headache, nausea and sometimes vomiting; neuronal toxicity is thought to underlie the feelings of intense lethargy seen commonly within 2 weeks of starting treatment. Acute encephalopathy may occur in patients with raised intracranial pressure fractions of brain radiation above 3 Gy. The usual daily radiation dose is 1.8–2 Gy. Encephalopathy is now seldom seen since these low-dose radiation fractions have been given and almost always patients are pre-treated with steroids.

Early-delayed toxicity

Acute toxicity can be followed by a longer period of lethargy and exhaustion lasting up to 3 months after treatment, known as early-delayed toxicity. Worsening of pre-existing deficits and seizures can occur. This condition is usually reversible with steroids but improvement is sometimes slow, over many weeks.

Late-delayed toxicity

Late-delayed effects include cognitive decline resulting from leucoencephalopathy, vascular damage and radiation necrosis (see above), the latter clinically and radiologically similar to recurrent tumour. These late-delayed effects become apparent between 6 months and even up to 20 years following treatment. Other late effects include changes in taste, hearing and vestibular function. Radiation necrosis, usually apparent between 6 and 24 months after radiation, can mimic tumour recurrence both clinically and radiologically. The estimated risk of necrosis is 5% following 64 Gy; some data suggest a lower threshold dose of 50–58 Gy. PWI and DWI can help distinguish between necrosis and tumour recurrence. ADC and rCBV measurements are also of some value (see above).

Other complications of cranial radiotherapy

Other late toxicity may become relevant if other normal structures are included in the high radiation dose volume, e.g. the optic chiasm, pituitary and skin. The lens is commonly treated to near-tolerance in frontal tumours, with a substantial risk of cataract. These toxicities can be avoided to some extent by planning and accurate shielding of normal structures. In some instances moderate dose irradiation will be unavoidable and patients must be warned of possible consequences.

Secondary tumours and vascular disease

In addition to direct neurotoxic effects, radiotherapy can cause second brain and exceptionally spinal tumours. Meningiomas, gliomas, schwannomas and cavernomas can develop years after treatment. Radiotherapy can also cause accelerated large vessel arterial disease, most commonly seen in young adults presenting with internal carotid artery occlusion after treatment in childhood for optic nerve or hypothalamic gliomas.

Spinal cord irradiation

Myelopathy, radiculopathy and plexopathy

Radiotherapy to the spinal cord is rarely associated with acute toxicity: however, a myelopathy may ensue in the months following treatment. Radiation myelopathy is usually late-delayed and presents either as a progressive myelopathy or as a lower motor neurone syndrome. This is most commonly seen in patients with Hodgkin's disease given mantle radiotherapy. Some patients seem especially susceptible to myelotoxic effects of radiotherapy and develop a severe cord syndrome after radiation doses well below usual tolerance.

Patients treated with axillary radiotherapy for breast cancer may develop a late-delayed radiation brachial plexopathy, distinguished from tumour recurrence by the absence of pain and sometimes the presence of fasciculation on electromyography.

Diagnosis of radiotherapy-induced toxicity

The development of neurological symptoms and signs should only be ascribed to the damaging effects of radiotherapy if the following conditions are met:

- The anatomy of the clinical signs corresponds to the radiation portals.
- The dosage and fractionation are sufficient to damage that particular area of the nervous system.
- The time elapsed between radiotherapy and development of the neurological syndrome is compatible with known effects of radiotherapy on the nervous system.
- Tumour recurrence has been excluded, particularly in the brain where clinical and radiological features of radiotherapy necrosis can be hard to differentiate.
- Other differential diagnoses, e.g. spinal intramedullary metastasis, paraneoplastic syndromes, CNS infection and malignant meningitis, have been excluded.

Radiotherapy and chemotherapy for high-grade gliomas

Radiotherapy for high-grade gliomas

The addition of radiotherapy to surgery is standard palliative management for patients with high-grade gliomas (WHO Grades III and IV). The degree of benefit varies between different prognostic groups; it is typically modest and measured in months. Several studies have demonstrated a dose response to radiation, with improved median survival when fractionated doses of around 60 Gy in 30 daily fractions are given compared to lower doses in the 45 Gy range. No convincing further improvement is apparent when doses are increased above 60 Gy, using either external beam or brachytherapy boost doses. This may be because a potential increase in tumour control is obscured by an increase in early radiation toxicity or because high doses given to a very localized field do not encompass the whole area at risk for recurrence. For patients in the best prognostic groups with WHO Grade IV gliomas, i.e. those with little deficit, addition of radiotherapy improves survival by 5–6 months but only to a median figure of 9–12 months. In patients with lower than median expected survival the impact of radiotherapy is even more modest and may be only a matter of weeks. Overall, functional deficit improves in one-third of patients and stabilizes the situation, if briefly, in half. In the poorest prognostic groups an alternative approach using shortened course, high-dose palliative radiotherapy regimes is sometimes advocated on the basis that this impinges less on quality of life in the remaining months. When discussing relative risks and benefits of radiotherapy, it is important to take into consideration the limited symptomatic improvement that can be anticipated, the rarity of a prolonged response and the lethargy, hair loss and risks of neurological deterioration resulting from radiation.

Chemotherapy for high-grade gliomas

The place of chemotherapy in first line treatment of high-grade gliomas has been assessed in many studies since the 1960s. These have included regimes in which chemotherapy is administered adjuvantly (following surgery and radiotherapy) or neoadjuvantly (prior to radiotherapy). Few have demonstrated a significant benefit in terms of survival compared with surgery and radiotherapy alone. The MRC Glioma Meta-analysis Group concluded that adjuvant chemotherapy given at or around the time of surgery and radiotherapy had a marginal benefit of 6% absolute improved survival at 1 year. The chemotherapy regimes were most commonly procarbazine, CCNU (lomustine) with vincristine (PCV), the most active combination of traditional chemotherapy in this disease. Common UK practice has been to give chemotherapy at first relapse rather than around the time of initial radiotherapy. The oral alkylating agent temozolomide has been used as an alternative to PCV and is currently being compared head-to-head with the older regime in recurrent high-grade gliomas. This approach – to save chemotherapy for recurrent disease – has been challenged recently both by new data and recognition of specific tumour subgroups that may be especially chemosensitive.

Concomitant chemotherapy for high-grade gliomas

Despite lack of evidence in favour of traditional adjuvant PCV chemotherapy overall in high-grade gliomas, recent data suggest a significant benefit for patients with WHO Grade IV astrocytomas (GBM) when temozolomide chemotherapy is given both concurrently with radiotherapy and subsequently adjuvantly for a further 6 months. These data support use of daily low-dose temozolomide throughout a 6-week course of radiotherapy followed by monthly 5-day courses for 6 months. Overall median survival, although modest, increased from 12.1 to 14.6 months; 2-year survival increased from 10% to 26%. The addition of chemotherapy produced some increased toxicity, although mild with no measurable impact on quality of life. An important issue was a high incidence of *Pneumocystis carinii* pneumonia during concomitant treatment necessitating prophylaxis with co-trimoxazole or pentamidine. This regime has rapidly become standard treatment for patients with GBM with good performance and who are considered to be able to tolerate combined treatment.

The situation for patients with WHO Grade III tumours is uncertain. Grade III cases have in any event a better prognosis than WHO Grade IV and therefore may experience late-delayed toxicity from combined chemo-radiation that offsets any potential survival benefits. An additional question is whether molecular analysis will enable identification of glioma patients who are more likely to respond to temozolomide. The mechanism of cytotoxicity of temozolomide relies on DNA base damage that can be repaired by a specific enzyme, O^6-methylguanine-DNA methyltransferase (MGMT). MGMT is responsible for removal of O^6-alkylguanine from DNA induced by alkylating mutagens/carcinogens. Levels of MGMT within tumour cells vary between GBM patients. Initial data suggest that patients with high levels of MGMT repair enzymes are less likely to benefit from the addition of temozolomide chemotherapy. Molecular and chromosomal analysis of all high-grade gliomas is likely to become a standard part of management.

Chemotherapy for relapsed disease in high-grade gliomas

Chemotherapy was until recently in the UK used almost exclusively at the time of relapse of high-grade gliomas. The standard approach in the UK has been the PCV combination regime in 6-weekly cycles. Response rates (temporary symptomatic benefit) are 20–30%. Radiological improvement and clinical response are associated with increased time to further progression. However, there are no data that suggest significant improvement in overall survival for the majority of patients. Toxicities from this regime include bone marrow suppression, liver function test abnormalities, neuropathy, skin rash and gastrointestinal upset. In most patients the regime is well tolerated; if it is not, it is rarely appropriate to continue in view of the poor response rates. Whether this regime represents the optimal approach to treating relapsed disease, or whether temozolomide is substantially better remains unresolved. Optimal chemotherapy for patients who have previously received adjuvant treatment with temozolomide is also not resolved. This situation is difficult because of the relative paucity of agents with well-documented response rates in this situation. An alternative approach if the recurrence is operable is to insert carmustine (Gliadel) wafers into the resection cavity. This tends to avoid systemic side-effects but may cause cerebral oedema and poor wound healing. Other potentially useful agents include carboplatin and taxol. Novel agents are being assessed, including the *c-kit* tyrosine kinase inhibitor imatinib (Gleevec), epidermal growth factor receptor (EGFR) signalling antagonists and anti-angiogenic agents. Of the latter, the monoclonal antibody bevacizumab has shown some promise in Phase II studies when combined with irinotecan and Phase III trials are currently underway.

Radiotherapy for low-grade gliomas

Several trials have examined dose response and timing of radiotherapy for WHO Grade II gliomas. WHO Grade I tumours are rarely treated with radiotherapy. Contrary to the situation in high-grade gliomas there is little evidence with WHO Grade II tumours for a dose response beyond 50 Gy. The timing of radiotherapy for these patients has also been contentious. Some centres have always advocated early postoperative radiotherapy on the basis that it is likely to be radio-biologically most effective when tumour volume is small and that the incidence of malignant transformation will be reduced. Others have felt that the long natural history of the disease means that such early intervention is unwarranted. This issue has been addressed in a randomized trial. The results suggest that while early irradiation to 54 Gy does not improve overall survival, time to progression is improved from 3.4 to 4.8 years in the treated group. Thus, many would now advocate early treatment in those patients at highest risk of progression, such as those with tumours in eloquent areas or for whom surveillance is inappropriate.

Radiotherapy is also used in patients with intractable seizures in the absence of tumour progression. There is an approximately 75% chance of seizure improvement. In one trial comparing radiotherapy with no radiotherapy for low-grade gliomas, 25% of patients who had been irradiated had seizures at 1 year, while nearly 50% who had not been irradiated had seizures.

The role of chemotherapy in low-grade glial tumours is not yet established so it is generally reserved for treatment of oligodendrogliomas particularly large volume tumours where the radiation field would be extensive or when radiotherapy has been given and there is transformation to a high grade.

Chemotherapy for anaplastic oligodendrogliomas

Oligodendroglial tumours are known to carry improved prognosis compared to high-grade astrocytic tumours. Recently, it has been found that an association with abnormalities of chromosomes 1p and 19q (see above) seems to define a group of oligodendroglial tumours that respond well to either chemotherapy or radiotherapy. Because many older studies did not distinguish this subgroup, these treatment-sensitive patients were probably an important source of heterogeneity. Current data suggest that response rates to nitrosurea-based chemotherapy in these anaplastic oligodendrogliomas (AO) is 60–70%. This is compared to figures of 20–30% for other high-grade gliomas and reflects the fact that about 70% of AOs have LOH at chromosomes 1p/19q associated with 100% chemosensitivity. The exact relationship between each of these chromosomal losses and the mechanisms underlying the chemo-sensitivity is unclear. However, despite this relative chemo-sensitivity, large clinical studies have not demonstrated a survival benefit for either neoadjuvant or adjuvant chemotherapy in this patient group when compared with patients given their first chemotherapy at relapse. Current practice for anaplastic oligodendroglioma is therefore to assess chromosome loss as a prognostic rather than a predictive factor. Surgery and radiotherapy remain the primary treatments. Chemotherapy tends to be reserved for relapsed disease.

Radiotherapy for meningiomas

The majority of meningiomas are benign, with recurrence rates frequently less than 10% after total excision. Radical surgery remains the mainstay of treatment.

A minority of meningiomas present management problems if they cannot be fully excised or if there are aggressive histological features suggesting a risk of recurrence. In these circumstances recurrence rates may be as high as 80% over 10 years. The role and timing of radiotherapy as adjuvant treatment in these circumstances is debated.

Several retrospective series have suggested that radiotherapy improves local control of these aggressive tumours, but no randomized series are available. In one retrospective series of WHO Grade I meningiomas, local recurrence rates following presumed total resection and subtotal resection were 52% and 77%, respectively, at 7 years median follow-up. Subtotal resection with radiotherapy achieved local control rates of 91% compared to 38% with subtotal resection alone. There was no influence on survival with adjuvant radiotherapy treatment. Although these data argue in favour of radiotherapy as adjuvant treatment after subtotal resection, they do not address its long-term side effects, particularly in younger age groups. Long-term risks include induction of a second tumour, pituitary failure and cognitive decline. Radiotherapy is therefore not offered routinely after subtotal resection of meningiomas because of these concerns. A common approach is to reserve radiotherapy for adjuvant treatment at first or subsequent relapse or in subgroups with higher risks of local relapse, including Grade II meningiomas or other atypical histology.

Whether or not radiotherapy is effective as primary treatment in circumstances where surgery is either impossible or associated with significant risks has not been clearly addressed. Retrospective series suggest that local radiotherapy as primary treatment may produce local control rates >90% in Grade I tumours. In individual patients this must be balanced against the likelihood of long-term sequelae of radiotherapy, especially relevant in patients with life expectancies beyond 10 years.

Newer radiotherapy planning techniques and radiosurgery can be used to reduce the volumes of normal brain irradiated in these patients, as these tumours can often be treated with a very small margin (5–7 mm) beyond visible tumour on MRI. However, there are no data that show the reduction in late toxicity by this approach.

Brain metastases: radiotherapy and chemotherapy

Treatment for most brain metastases is purely palliative. Chemosensitive tumours such as germ cell neoplasms and trophoblastic disease are rare examples in which cure may be achieved with aggressive treatment. In other cases the management of these patients must be carefully considered in the context of their overall disease burden and prognosis. Several groups have attempted to categorize these patients into prognostic groups with the aim of predicting those most likely to benefit from treatment. Clearly, these decisions depend on having accurate and up-to-date information about disease status within and outside the brain and a careful assessment of the patient's performance status.

Broadly, treatment options in this group lie between surgical resection and radiotherapy for almost all patients. In some groups with no previous malignant history or in whom there is diagnostic doubt, biopsy may be necessary to confirm the diagnosis even if no other surgical intervention is planned. The most difficult group in this respect are elderly patients with concurrent medical conditions and no obvious primary site. In these cases even biopsy may not be appropriate.

However, caution in diagnosis is essential: about 10% of patients with suspected brain metastases harbour unsuspected histology including abscesses, inflammatory/infective lesions (such as neurocysticercosis) or gliomas.

Resection of brain metastases is the only treatment that can offer rapid relief of symptoms from mass effect. It is indicated particularly for single lesions in the posterior fossa causing obstructive symptoms and solitary hemisphere lesions with controlled systemic disease. It is usually contraindicated in cases with several brain lesions, as surgical results are so poor, a reflection that many patients will die in any event from uncontrolled disease outside the brain within a few months of surgery.

A further question is WBRT following resection. Available data suggest that WBRT improves local (brain) control but not overall survival. The standard approach is to add a short course of palliative radiotherapy, e.g. 20 Gy given in five daily fractions of 4 Gy in 1 week.

Radiotherapy alone to the whole brain has also been standard treatment for patients with unresectable metastatic brain lesions and/or with uncontrolled systemic disease. However, the palliative value of short course radiotherapy has been questioned. It is hard to know whether improvements are a result of the radiation or concomitant use of steroids.

Radiosurgery for brain metastases

Radiosurgery can be appropriate in patients with one to three lesions that are not accessible surgically. Most practitioners limit the size of lesions to be treated to those less than 4 cm diameter because of the high radiation doses administered.

Chemotherapy for brain metastases

In all CNS malignancies the blood–brain barrier is at least a theoretical limitation to drug penetration, but the exact contribution that this makes to the poor response to chemotherapy is unclear. A distinct minority of tumour types presenting as brain metastases are known to demonstrate clinically useful chemo-sensitivity. These metastases include small cell lung cancer (SCLC), germ cell tumours and breast cancer. Response rates up to 66% at first treatment in SCLC have been documented. Some studies have shown that breast cancer brain metastases can respond to agents used for systemic disease in over 50% of cases. Median survivals after chemotherapy are similar to those after WBRT. Therefore, chemotherapy is probably most appropriate for those who are relatively chemo-naïve, as many patients will have been exposed to multiple chemotherapy agents prior to presenting with brain metastases.

New approaches are clearly needed in the treatment of brain metastases. Combinations of conventional chemotherapy agents with molecularly targeted drugs such as gefitinib (Iressa), a tyrosine kinase inhibitor, have been shown to produce responses at primary tumour sites such as lung tumours and may help metastases. Temozolomide has also been studied alone or in combination with radiotherapy. New approaches to radiosensitization with agents such as COX2 inhibitors are being investigated.

The use of dexamethasone to improve symptoms of raised intracranial pressure and focal deficits is part of standard treatment of brain metastases and brain malignancies generally. The optimal dose has not been defined but some data suggest that low-dose dexamethasone (4 mg/day) is as effective as high dose (16 mg/day) in the majority.

Radiotherapy and chemotherapy for spinal tumours

Ependymomas

The most common primary spinal intramedullary tumour in adults is ependymoma, which makes up 50–60% of diagnoses and occurs most commonly in mid adult life. It is common for the diagnosis to be made after months or years of slowly progressing symptoms. Surgery is usually the first treatment, to make a histological diagnosis and attempt gross removal. A postoperative MRI at 2–3 months is often recommended to record residual disease and serve as a baseline for follow-up. In low-grade fully resected tumours, recurrence rates are low, in the region of 5–10%. However, this does not fully take in to account the problems of defining grade and extent of resection in these tumours. A recent series suggests that local relapse rates may be higher than generally appreciated at long-term follow-up: there is a significant recurrence rate beyond 5 years, with only 50% of patients progression free at 10 years. Local postoperative radiotherapy is usually recommended in all patients.

There are not enough data available to be able to assess whether there is a dose response to radiation in these circumstances. Most studies reporting outcome after radiotherapy are small series that use a narrow range of doses. It is clear though that recurrences distant from the original ependymoma site are very rare, therefore extended field or cranio-spinal treatments are not recommended unless there is evidence of distant spread. The maximum radiation dose that can be administered is limited by the tolerance of the spinal cord. Current practice is to treat low-grade ependymomas to a dose of 50 Gy in 1.8 Gy fractions and higher grade tumours to 54 Gy.

Astrocytomas of the cord

The only other primary intrinsic cord tumours that occur with any frequency are astrocytomas. They are most often fibrillary, low-grade subtypes. Clinically and radiologically these tumours often present in a very similar way to ependymomas although they may be less well defined than a typical ependymoma. Surgery is often not appropriate in patients with significant neurological deficit or with high-grade lesions for whom extensive resection does not improve survival. Prognosis is less good than in ependymoma. High-grade tumour cases have a median survival around 20 months.

No large studies have addressed the role of radiotherapy in spinal glioma patients. Small series suggest that less extensive surgery plus postoperative radiotherapy can produce local control in around 50% of patients with low-grade tumours, with 5-year survival rates around 60%.

Chemotherapy for intrinsic cord tumours

Overall there are few data on the chemo-sensitivity of intrinsic cord tumours. The literature addressing responses to chemotherapy in intracranial ependymoma suggests a low response rate to combination chemotherapy regimes and no evidence that it improves survival. Low chemo-sensitivity has been attributed to over-expression of *MDR1* (multi-drug resistance gene) in ependymoma tissue. Paediatric literature suggests a modest response to chemotherapy in high-grade spinal astrocytomas. However, these small studies do not allow firm conclusions to be drawn about responses in adult patients.

Radiotherapy and chemotherapy for spinal metastases

Following decompressive spinal surgery, local radiotherapy is often used as palliative treatment. Chemotherapy, depending upon the nature of the primary, is sometimes appropriate.

Non-gliomatous tumours

This section summarizes features of various tumours of the brain and cord referred to in Table 20.1.

Pituitary tumours

The pituitary is a tiny organ, uniquely supplied by two separate circulations: the systemic and portal systems. The sellar region is the site of many disease processes (Table 20.3) of which pituitary tumours account for the majority.

Pituitary tumours represent 10–15% of all intracranial neoplasms. They can be classified by biological behaviour, size or histological and functional criteria (Tables 20.4 and 20.5).

Biological behaviour

Tumours may be either benign, invasive adenomas or carcinomas. Benign forms are most common but up to 50% show evidence of capsule invasion and about one-third invade the dura or the sphenoid sinus. Pituitary carcinomas are exceedingly rare.

Table 20.3 Lesions of the sellar region.

1 Tumours
Primary pituitary tumours
Craniopharyngioma
Meningioma
Germ cell tumours
Glioma – hypothalamic, optic nerve
Granular cell tumours
Lymphoma
Ependymoma
Metastases

2 Others
Cysts – Rathke's pouch, epidermoid, dermoid
Empty sella syndrome
Carotid and anterior communicating artery aneurysm
Lymphocytic hypophysitis

3 Granulomatous disease
Sarcoidosis
Wegener's granulomatosis
Histiocytosis X

4 Infections
Pituitary abscess – bacterial or fungal infection
Tuberculosis
Syphilis

Size

Microadenomas are less than 10 mm and macroadenomas greater than 10 mm in diameter. Microadenomas are the more common and typically lie within the sella but can extend into the suprasellar space. Macroadenomas as they enlarge erode the sellar floor and eventually cause its destruction. The anatomy of adenomas is defined most accurately by MRI which clearly displays anterior and posterior lobes of the pituitary and its relation to the paranasal air and venous sinuses.

Histology

Cells forming a pituitary adenoma are defined by histological, hormonal and immunological characteristics. Acidophilic and chromophobe cells usually produce prolactin (Prl), growth hormone (GH) or thyroid-stimulating hormone (TSH). Basophilic cells produce adrenocorticotrophic hormone (ACTH), β-lipotrophin, luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Functional criteria

Radioimmunoassay allows precise measurement of pituitary hormones. The most common type of pituitary adenoma (approximately 30%) are functionally inactive and typically chromophobe adenomas. Of those adenomas that secrete hormones, 60–70% produce prolactin, 10–15% secrete growth hormone and some

Table 20.4 Classification of pituitary tumours.

Cell of origin	Hormone	Clinical features
Non-functioning	None	Cause symptoms only when they extend beyond the sella Most common type of macro-adenoma (30–35%)
Lactotroph	Prolactin	Typically intrasellar but may enlarge The most common hormone producing pituitary adenoma (40% of cases)
Corticotroph	ACTH	Secretion of ACTH leading to Cushing syndrome (approx. 10% of cases) Usually confined to sella. May enlarge and become invasive particularly after adrenalectomy (Nelson syndrome)
Somatotroph	GH	Gigantism in children and adolescents; acromegaly in adults Suprasellar extension relatively common Approximately 15% of cases
Thyrotroph	TSH (also occasionally GH & Prl)	Hyperthyroidism without TSH suppression May be large and invasive Rare, approx. 1–2%
Gonadotrophin	FSH or LH	Usually non-functioning May result in ovarian overstimulation, increases testosterone level, testicular enlargement or pituitary insufficiency due to compression of the stalk or destruction of pituitary tissue by the tumour Uncommon
Plurihormonal	More than one hormone	May have one cell population producing two or more hormones or two or more distinct cell types
Carcinoma		Usually functional (ACTH and Prl producing) Varying degrees of nuclear atypia and cellular polymorphism but often high mitotic rate and cell proliferation Rare (<0.2%)
Metastatic		Breast and lung cancer are most common neoplasms metastasing to pituitary. Also lymphoma, leukaemia, melanoma and prostate

ACTH, adenocorticotrophic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; Prl, prolactin; TSH, thyroid-stimulating hormone.

Table 20.5 Endocrine syndromes associated with pituitary tumours.

Prolactinoma (hyperprolactinaemia)	Amenorrhoea, infertility, galactorrhoea, loss of libido, erectile dysfunction
Corticotroph (Cushing's syndrome)	Obesity with centripetal fat distribution, hirsutism, abdominal striae, acne, hypertension, glucose intolerance, muscle wasting and weakness, osteoporosis, neuropsychiatric disturbance, immunosuppression
Nelson's syndrome	Due to growth of residual tumour after bilateral adrenalectomy in Cushing's patients Occurs when high plasma ACTH levels persist despite adequate glucocorticoid replacement Hyperpigmentation, mass effect. Tumours resistant to therapy
Growth hormone (acromegaly or gigantism)	Growth of hands and feet, prognathism, coarsening of facial features, carpal tunnel syndrome, diabetes, osteoarthritis, arthralgia, excessive sweating, obstructive sleep apnoea
TSH (thyrotoxicosis)	Features of thyrotoxicosis, weight loss, anxiety, palpitations, tremor, insomnia, menorrhagia
Gonadotrophin	Rare: testicular enlargement, ovarian stimulation

5% secrete ACTH. Gonadotrophin and TSH secreting tumours are exceptionally rare.

Clinical presentation

Pituitary adenomas present typically with chronic mass effects, particularly affecting visual structures, chronic headaches, endocrine abnormalities resulting from hormonal hypersecretion and/or hyposecretion, or a combination of these factors. Occasionally, acute pituitary apoplexy occurs. Macroadenomas are the most common cause of chiasmal compression in adults and cause bi-temporal hemianopia. Partial patterns of visual loss develop, depending on the anatomical relationship of the tumour and the chiasm, leading to asymmetrical superior bitemporal hemianopia or optic nerve involvement. Oculomotor palsies develop if the pituitary adenoma extends laterally into the cavernous sinus through which pass cranial nerves III, IV and VI, the first two divisions of V and the sympathetic nerves to the eyes. Extension into a temporal lobe can lead to epilepsy. Rarely, hydrocephalus may occur because of direct compression of the third ventricle leading to raised intracranial pressure or erosion through the sella to cause CSF rhinorrhoea. Compression of the internal carotid artery may lead to cerebral ischaemia. Hypothalamic invasion may affect temperature regulation and cause hypersomnolence, autonomic dysregulation and diabetes insipidus.

Hormonal abnormalities caused by pituitary adenomas depend on the cell type and hormone produced (Table 20.5).

Pituitary apoplexy

Pituitary apoplexy results from acute haemorrhagic or ischaemic infarction of the pituitary, often with a previously unrecognized secreting or non-functioning pituitary adenoma. This is believed to occur because a tumour outgrows its blood supply. Extensive haemorrhagic infarction leads to mass effect in the suprasellar space and cavernous sinus. Apoplexy is rare and presents with sudden headache, meningism, vomiting, visual loss, ophthalmoplegia, visual field defect and occasionally impairment of consciousness. Secondary pituitary dysfunction and hyponatraemia can follow. The CSF shows evidence of haemorrhage with a pleocytosis and elevated protein. Predisposing factors include pregnancy, postpartum haemorrhage, trauma, diabetic ketoacidosis, radiotherapy and angiography. The condition may occur after bromocriptine has been started. Steroids are required urgently to treat pituitary apoplexy. Surgery may be necessary. Panhypopituitarism commonly follows and requires lifelong replacement therapy.

Management of pituitary tumours

Management of pituitary tumours is directed at normalizing hormonal secretion, reversing endocrine manifestations of excess secretion and preventing progressive neurological deficit, especially visual loss. Treatment options include surgery, medical management and radiotherapy. The choice is determined by the histological typing of the tumour, the nature of its hormonal expression, the size and its extension into surrounding structures. Transphenoidal pituitary surgery is the most widely employed approach, particularly for non-functioning macroadenomas causing chiasmal compression. It allows direct visualization of the gland and tumour and is well tolerated. It is successful in debulking tumours even if there is a considerable suprasellar extension and regrowth is uncommon. Advances in MRI, using high-field techniques, allow peri-operative assessment of the completeness of surgery and the planning of postoperative management. However, transphenoidal surgery is less effective if there is an hour-glass narrowing between the intrasellar and suprasellar component of the tumour or if there is infection within the sphenoid sinus. In these situations, surgery via a craniotomy using a subfrontal approach may be necessary. Radiotherapy is an effective adjunct to the treatment of pituitary tumours, particularly if surgery is contraindicated or has not completely eradicated the tumour. The responses are relatively slow and may require up to 10 years for a complete and sustained remission; furthermore, there remains a risk of the development of hypopituitarism. Stereotactic or gamma knife radiotherapy for resistant tumours is an important adjunct if complete resection cannot be achieved surgically but side effects include radiation-induced optic neuropathy, hypopituitarism and necrosis of the temporal lobe.

Surgical treatment is preferred for GH, TSH and ACTH producing and endocrinologically inactive tumours. However, GH secreting tumours may be treated initially with medical treatment using the GH receptor antagonist, pegvisomant, or somatostatin analogues (e.g. ocreotide, tancreotide) which normalize GH level and decrease the tumour size in refractory acromegaly. Adjuvant radiotherapy is used following transphenoidal surgery if the tumour is extensive. The other complications of acromegaly are managed symptomatically. Asymptomatic prolactinomas do not require therapy as progression is uncommon. Treatment is indicated either because of endocrine or mass effect. Prolactinomas are usually treated medically with dopamine agonists, e.g. carbergoline or bromocriptine, which are effective in shrinking the size of the adenoma and lowering serum prolactin levels. Prolactin levels are often maintained after the drug has been discontinued but if medical therapy fails then transphenoid surgery and radiotherapy may be indicated. Surgery is required if the tumour does not respond to medical treatment, if pituitary apoplexy occurs or if the patient is not able to tolerate long-term medical treatment.

Pituitary carcinoma requires radical resection with adjuvant radiotherapy and chemotherapy, dependent on histological subtype.

Craniopharyngiomas

These are slow-growing benign extra-axial cystic tumours in the parasellar region. Cysts, sometimes multiple, contain thick proteinaceous material, often shiny because of a high content of cholesterol crystals. A cyst can extend in any direction and project into the hypothalamus, basal cisterns, third ventricle, cerebellopontine angle, posterior fossa or the foramen magnum. Presentation is usually as a slow-growing tumour but there may be a sudden onset with rapid deterioration because of increase in volume or rupture causing a chemical meningitis or ventriculitis. The most common symptoms are headaches, visual disturbance and endocrine dysfunction. The clinical features may be similar to pituitary adenoma with progressive chiasmal compression except that craniopharyngiomas typically compress the superior aspects of the chiasm and cause inferior field defects. There may also be involvement of the optic nerves if the tumour is prechiasmal causing progressive optic atrophy with impaired acuity and constriction of the fields. Endocrine dysfunction is brought about by involvement of the pituitary stalk leading to hypothyroidism, adrenal insufficiency, diabetes insipidus, growth failure and reduced sexual drive. Compression of the third ventricle leads to hydrocephalus and raised intracranial pressure with headache and papilloedema. Secondary hypothalamic involvement is common leading to hyperphagia and obesity. Craniopharyngiomas can infiltrate the frontal lobes, mamillary bodies and limbic system, eventually spreading to the Sylvian fissure leading to emotional, psychiatric and behavioural disturbances, apathy and short-term memory deficits.

Radical cure is difficult to achieve because the cysts are often multiple, adherent and inaccessible. Gross total surgical removal is the treatment of choice but carries considerable morbidity because of the risks of incomplete removal, cyst rupture and hypothalamic damage. Recurrence is common. Incomplete removal carries less morbidity but must be followed by postoperative radiotherapy. The risks of side effects related to radiotherapy are relatively low but intellectual decline, optic neuropathy and hypothalamic damage may occur. There may also be residual endocrine deficits including diabetes insipidus and cognitive impairments. New techniques of intracyst chemotherapy, stereotactic radiotherapy or internal irradiation are also used. Prognosis is highly variable with a significant morbidity and mortality following local extension. A poor outcome may be predicted by a young age of onset, pre-operative visual impairment, papilloedema, hydrocephalus and hypothalamic involvement. Subtotal resection, tumour calcification and adhesive tumour wall also predict a poor outcome.

Primary CNS lymphomas

The term lymphoma encompasses a large heterogeneous group of malignant lymphoid neoplasms. When these tumours are confined to the brain, spinal cord or leptomeninges they are known as primary CNS lymphomas (PCNSL). These account for about 3% of primary CNS tumours, occurring predominantly in older people with a slight male preponderance. Immunosuppressed patients, most commonly HIV-positive, are about 1000 times more likely to develop PCNSL than immunocompetent adults. Indeed, PCNSL was previously very rarely seen at all before the AIDS epidemic. However, there is also sound evidence that the incidence of PCNSL has increased in the immunocompetent population over the last two decades, particularly in the over 65 age group.

PCNSL usually present as either solitary or multiple mass lesions with raised intracranial pressure, progressive focal neurological deficit and seizures. Intracranial lesions are usually supratentorial; more than 60% are periventricular, involving the splenium, corpus callosum, basal ganglia and the thalamus. Rarely, the tumour invades and proliferates within the small vessels of the brain, spreading along intravascular spaces. This is known as intravascular lymphoma or malignant angioendotheleliomatosis. This presents as either progressive multifocal cerebrovascular events or as a subacute encephalopathy. Very rarely, PCNSL develop in the meninges, leading to a progressive leptomeningeal syndrome with cranial nerve palsies, hydrocephalus and myelopathy. Ocular lymphoma presenting with visual loss can predate the appearance of intracranial lymphoma.

The majority of PCNSL are high-grade B-cell lymphomas. Anaplastic large cell and T-cell variants are also described. They rarely metastasize outside the CNS but may spread along CSF pathways into the spinal cord. Approximately 20% of cases have intraocular involvement at diagnosis. Even in the majority of patients who have a single supratentorial mass lesion, the disease should be regarded as multifocal from outset. There is therefore no benefit in resection of the tumour except where there is life-threatening intracranial hypertension.

Diagnosis is usually suspected from initial imaging which shows typically one or several homogeneously enhancing masses, often in a periventricular location. In immunocompetent patients, in about 30% of cases the tumours are multiple, rising to some 50% in AIDS patients. Once the diagnosis is suspected, steroids should be withheld because of their lympholytic properties until a stereotactic biopsy has been carried out, unless the patient has life-threatening intracranial symptoms. There are many reported cases of these tumours disappearing after even a few days on steroids. This phenomenon is not diagnostic of CNS lymphoma; it is seen also with inflammatory masses, e.g. acute demyelination and even with gliomas.

The diagnosis may be confirmed from a CSF sample if the brain lesion is sufficiently small to allow safe lumbar puncture. CSF cytology is positive in about 30% of cases and the sensitivity increases with two or three lumbar punctures. Flow cytometric studies and polymerase chain reaction (PCR) looking for clonal rearrangements of immunoglobulin heavy chains can improve sensitivity but are not universally available. In situations where CSF is negative or a lumbar puncture cannot be carried out for fear of coning, a stereotactic biopsy will usually establish the diagnosis. A contrast-enhanced MRI of the spine should also be carried out to look for leptomeningeal tumour deposits. Open craniotomy and resection can lead to seeding of tumour cells into the leptomeningeal space and does not confer any survival benefit. Once the diagnosis is suspected, the patient's HIV status should be determined and the eyes examined by an experienced ophthalmologist for evidence of intraocular disease. Asymptomatic ocular involvement occurs in some 20% of patients and specific additional treatment may be required. Staging body CT and bone marrow aspirate are seldom required as systemic lymphoma is found rarely in PCNSL. Such a finding has no effect on subsequent disease course. Serum LDH is often greatly raised, sometimes useful as a diagnostic pointer and as a prognostic factor in PCNSL.

Current treatment of PCNSL is based around the use of high-dose intravenous methotrexate (HDMTX: ≥ 1 g/m^2) regimens followed by whole brain with or without spinal or ocular radiotherapy. In an effort to intensify chemotherapy and avoid the use of radiotherapy altogether (to minimize neurotoxicity), some centres have treated good performance patients with HDMTX alone followed by myeloablative chemotherapy and then autologous stem cell rescue. Long-term data have not been published. The additional benefit of intrathecal chemotherapy either via the lumbar route or via an Ommaya–Rickman reservoir directly into the ventricles is also not proven. WBRT in combination with corticosteroids leads to a response in about 70% of patients. This regimen is best reserved for elderly patients with poor performance status who would otherwise not tolerate HDMTX-based therapies.

The major dilemma facing oncologists arises in patients over the age of 60 years in whom the combination of methotrexate and WBRT is associated with an almost 100% risk of cognitive decline, ataxia and incontinence 1–2 years after treatment. This has led to the development of protocols based around chemotherapy alone although there is a risk of renal and bone marrow failure with these intensive regimens. Furthermore, as there are no randomized Phase III studies which prove that this can produce a long-term survival benefit, our own practice has been to irradiate to a dose of 30 Gy after obtaining radiological remission with chemotherapy.

The prognosis depends on age and performance status, as with other CNS tumours, but also on the extent of spread along CSF pathways and whether or not the patient is HIV-positive. Average survival of elderly patients treated with steroids alone is in the region of 6 months, increasing to 1 year with the addition of radiotherapy. This rises to 2 years in those under the age of 60 years. The combination of HDMTX chemotherapy followed by radiotherapy in patients under the age of 60 years is associated with 5-year survival rates of 65%, clearly much higher than any survival for high-grade gliomas.

Primitive neuroepithelial tumours and medulloblastomas

Primitive neuroepithelial tumours (PNET) are the second most frequent childhood primary brain tumour (about 20% of brain tumours) after astrocytomas but account for less than 1% of adult brain tumours. They are highly malignant (WHO Grade IV) and present in the brainstem as medulloblastomas, in the pineal as pineoblastomas and supratentorially as PNETs. Clinical features are non-specific but include gait ataxia, headache, vomiting and visual loss resulting from hydrocephalus. Children tend to have midline tumours that are well-defined and enhance homogeneously, whereas in adults tumours usually arise within the cerebellar hemispheres and are poorly enhancing. These tumours frequently metastasize within CSF pathways and therefore all patients require staging with MRI of the spine, ideally prior to surgery, as well as CSF examination either prior to surgery or 10–14 days after. Postoperative imaging to determine the extent of resection should be carried out ideally within 24–48 hours after surgery.

There are several histological variants including the classic (undifferentiated) medulloblastoma (the most common in adults), desmoplastic nodular and large cell (anaplastic), the latter associated with a particularly poor prognosis.

The main adverse factors in children are age less than 4 years, postoperative macroscopic residual disease >1.5 mL and CSF metastases. There has been a dramatic increase in survival in children with medulloblastoma over the last two decades from 4.9 to 10 years. Current therapy for children comprises craniospinal irradiation (CSI) and now also includes the routine use of adjuvant chemotherapy which increases 3-year event-free survival by about 10%. The data in adults are limited. Hydrocephalus is a poor prognostic factor.

The majority of reported cases of adult medulloblastoma (MB) come from retrospective studies from single institutions spanning many decades. It is therefore difficult to draw firm conclusions about the best treatment. However, certain principles are clear, namely the need for maximal resective surgery followed by CSI. What is not clear is whether CSI is adequate treatment alone for good prognosis patients and whether adjuvant chemotherapy improves survival.

Surgery has three aims – histological diagnosis, maximal safe tumour resection and relief of hydrocephalus, thus avoiding the need for a CSF diversion procedure with attendant risks of upward brainstem herniation, CSF dissemination and infection. Mortality should be less than 1%, morbidity 5–10%, with the most feared complication being cerebellar mutism. This is thought to arise from damage to the dentate nuclei but it gradually improves, although it does delay the start of adjuvant radiotherapy.

All patients are then treated with CSI, usually 36 Gy to the whole neuraxis followed by a boost to the posterior fossa of 18–20 Gy. Higher doses (45 Gy) are given to nodular metastases in the spine.

The role of chemotherapy is not yet established for adults with MB, as standard treatment (surgery plus CSI) yields a 60% 5-year progression-free survival. There is a perception that radiotherapy is less harmful to adults than to children in the long term and that survival benefit from chemotherapy in adults is less convincing than in children. However, most neuro-oncologists would treat high-risk adult MB patients with adjuvant chemotherapy. The most commonly used protocol in children is the Packer regimen which consists of weekly vincristine during CSI followed by eight cycles of CCNU, cisplatin and vincristine. The dose-limiting toxicity is peripheral neuropathy, hearing loss, renal failure and myelosuppression. In adults, there is some evidence to suggest that carboplatin, vincristine and ifosfamide (or cyclophosphamide) may be less toxic than the Packer regime.

Relapse in adult MB patients occurs in 20–50% by 5 years and is usually in the posterior fossa or in the spine. Treatment at relapse is therefore directed at resection or highly focused radiotherapy (e.g. stereotactic radiosurgery) to the posterior fossa followed by high-dose myeloablative chemotherapy and stem cell rescue. Unfortunately, almost all patients experience eventual recurrence either in the CNS or at distant non-CNS sites and succumb.

Overall survival ranges are 25–85% at 5 years and 35–50% at 10 years. Clinical trials are needed for adult patients, but until further results become available we must be guided by paediatric trials.

Pineal region tumours

A variety of tumours occur in the pineal region (Table 20.6), including germ cell tumours, non-germ cell tumours or pineal parenchymal tumours (pineocytoma and pineoblastoma) as well as gliomas and metastases.

The clinical syndromes associated with pineal region tumours are determined by the close anatomical relationship of the gland with the quadrigeminal plate and midbrain tectum ventrally, the third ventricle rostrally and the cerebellar vermis caudally. Typical syndromes include:

Table 20.6 Tumours of the pineal region.

Tumours of pineal origin (20%)
Pineocytoma
Pineoblastoma

Tumours of germ cell origin (>50%)
Germinoma

Non-germinomatous germ cell tumours
Teratoma
Embryonal carcinoma
Choriocarcinoma
Yolk sac tumour

Tumours of supporting or adjacent tissues
Glioma
Ganglioneuroma
Ganglioglioma
Meningioma

Non-neoplastic cysts
Arachnoid cyst
Pineal cyst

Vascular lesions
Aneurysm of vein of Galen
AVM
Cavernous malformation

AVM, arteriovenous malformation.

- Obstructive hydrocephalus: headache, nausea, vomiting and obtundation;
- Parinaud's syndrome: vertical gaze palsy, light-near dissociated mid-point pupils, loss of convergence and convergence-retraction nystagmus (Chapter 13); and
- Ataxia: caused by involvement of the superior cerebellar peduncle.

Germ cell tumours can produce diabetes insipidus, amenorrhoea, growth arrest and pseudo-precocious puberty. The diagnostic work-up of a pineal region tumour includes a gadolinium-enhanced MRI scan and tumour markers in serum and CSF alpha-fetoprotein (AFP) and human chorionic gonadotrophin (βHCG). High levels are pathognomic of malignant germ cell tumours and obviate the need for biopsy.

There is a high morbidity and mortality associated with pineal region surgery and thus debate about the pros and cons of biopsy alone versus open resection. The ultimate choice of procedure will depend largely on the individual surgeon but, as a general rule, a stereotactic biopsy is preferred where there is disseminated disease, clearly invasive malignant tumour or the patient has multiple other medical problems. The mortality and morbidity of stereotactic biopsy in modern series is around 1.3% and <1.0%, respectively. In contrast, open resection should be reserved for patients with benign lesions, in whom surgery can be curative or rarely for debulking of malignant tumours, particularly where the biopsy diagnosis has been hampered by small amounts of tissue or has been inconclusive.

The subsequent treatment and prognosis depends much on histology. Germinomas are exquisitely sensitive to radiotherapy and are associated with good long-term survival. Patients with non-germinomatous germ cell tumours have a significantly worse prognosis and are usually treated with a combination of chemotherapy and radiotherapy. Pineoblastomas are managed like medulloblastomas with a pre-operative MRI spine and CSF, which if negative should be followed by maximal tumour resection. If either of these is positive, then the risks of surgery probably outweigh the benefits and patients should be treated with CSI and chemotherapy.

Germ cell tumours

Germ cell tumours arise from primitive embryonic cells and usually present as ovarian or testicular tumours. The CNS is the second most common extragonadal site for germ cell tumours (after the mediastinum). They generally arise in the midline in the region of the pineal gland and the suprasellar region, accounting for approximately 50% of pineal tumours. Each of the histological germ cell variants are derived from cells of a normal stage of embryonal development and may be classified as follows:

1 Undifferentiated germ cell tumours derived from primordial germ cells:
   - Germinoma.

2 Differentiated non-germinomatous germ cell tumours:
   - Teratoma;
   - Embryonal carcinoma;
   - Endodermal sinus tumour (yolk sac tumour);
   - Choriocarcinoma.

Germinomas are histologically identical to testicular seminomas and are not usually associated with raised CSF tumour markers. They are extremely radio-sensitive and this is the mainstay of treatment although chemotherapy may be necessary if the lesion is extensive or if there is a relapse. The prognosis of germinoma is better than non-germinomatous germ cell tumours with estimated 5-year survival rate of 75%. Spinal cord seeding may occur in up to 15% of patients but extraneural spread is uncommon.

Non-germinomatous germ cell tumours of the pineal region present in the same way as germinomas with features of raised intracranial pressure resulting from hydrocephalus, Parinaud syndrome and brainstem or cerebellar compression. They have a mixed density on MRI and CT scan and often present as large cysts or areas of calcification with distinct margins. Occasionally, formed tissue may be identified within the cyst and more aggressive non-germinomatous germ cell tumours show heterogeneous enhancement. Choriocarcinoma may show extensive haemorrhagic change.

Tumour markers may be valuable in germ cell tumours. AFP and βHCG are commonly produced by non-germinomatous germ cell tumours and may be measured in the serum and CSF. Elevation of AFP suggests the presence of a malignant non-germinomatous germ cell tumour but these tumour markers are not highly sensitive as some tumours do not produce them and others are of mixed histology. Markers are of some value if present in assessing response to treatment. βHCG is elevated in choriocarcinoma.

The most effective treatment of non-germinomatous germ cell tumours is with a combination of chemotherapy and extensive radiotherapy but the results are variable. Long-term prognosis is much worse than germinoma.

Chordomas

These are rare tumours arising from remnants of the embryonic notochord and may therefore develop at any point along the length of the neuraxis, in particular the skull base and clivus, vertebral column and sacrum. They are aggressive malignant tumours which invade locally into bone and soft tissues and occasionally metastasize to distant sites. Patients usually die of locally recurrent disease. Clival chordomas present with headache and diplopia caused by VIth nerve palsy. This may progress to involve the Vth nerve and then the lower cranial nerves with vertigo, tinnitus and bulbar palsy causing dysphagia and hoarseness. Rarely, brainstem compression may occur with pyramidal tract dysfunction, ataxia and emotional lability. Autonomic symptoms such as sphincter disturbance can occur. Chordoma is the most common neoplasm of the sacrum and it may often be extensive before diagnosis. Slowly progressive low back pain with radicular or sciatic radiation involves the sacral nerve roots leading to peri-anal numbness, sphincter disturbance with urinary retention, incontinence and impotence. Involvement of the true vertebrae is uncommon. There may be bone destruction and infiltration into the paraspinal soft tissues. Dorsal expansion leads to nerve root displacement with severe localized radicular pain and sensory loss. Chordomas arising in the cervical region may cause direct oesophageal compression and rarely myelopathy.

Imaging of clival chordomas on CT shows tumour calcification, eroded bone and focal areas of hyperintensity and hypointensity within the tumour. On MRI the margins are clearly delineated; T2 shows hyperintense areas with extension either anteriorly into the paranasal sinuses and nasophrynx or posteriorly towards the brainstem.

The prognosis is variable with a better outlook for chordomas in the clivus or sacrum than in the vertebral column. Morbidity and mortality occurs because of the erosive nature of the tumour and the location within eloquent regions of the brain and skull base. Chordomas are difficult to treat because of their infiltrative behaviour and complete resection is often not possible. Partial resection is usually combined with radiotherapy to try to eradicate residual disease, but these tumours are highly radio-resistant. For this reason there is interest in the use of high-energy proton beam therapy. The advantage of proton therapy over standard radiotherapy given by a linear accelerator is that the proton beam can be very precisely targeted onto the tumour with a rapid fall-off of dose at the margins and normal surrounding tissue. There are no convincing data however that suggest protons are superior to standard radiotherapy in terms of overall survival. The overall 5-year survival is approximately 65% – older women with large tumours tend to have the worst prognosis.

Chondrosarcomas

Chondrosarcomas resemble chordomas superficially in that they present as a skull-base tumour causing cranial nerve compression with facial weakness or sensory loss, hearing impairment, vertigo or bulbar involvement, but they have a consistently better prognosis. Management is by surgical resection – as with chordomas. These tumours are relatively resistant to radiotherapy.

Dermoids and epidermoid cysts

These are cystic lesions arising from inclusion of ectodermal tissue during neural tube development and sequestration cysts which may accompany dysraphism, e.g. spina bifida with communication to the skin surface through a sinus tract. Dermoid cysts contain hair follicles, sweat glands and sebaceous glands. They arise in the posterior fossa in the region of the midline, vermis or fourth ventricle or in the suprasellar cistern and present with local mass effects or by rupture of their contents into the CSF causing granulomatous meningitis. Management is by total surgical excision. Incompletely resected cysts may recur.

Epidermoid cysts are more common and arise in the cerebellopontine angle or middle cranial fossa causing mass effect, facial pain and cranial nerve deficits. Surgical removal of epidermoid cysts may be difficult because of their tendency to spread along cranial nerves but is usually curative. Very rarely epidermoid cysts undergo malignant transformation.

Haemangioblastomas

These are benign, cystic, highly vascular tumours. They are formed by vessels that range in size from small capillaries to large vessels and there may be one or more associated cysts. They generally arise in the posterior fossa and cause symptoms either because of raised intracranial pressure or cerebellar dysfunction. Less commonly there may be brainstem involvement leading to motor and sensory deficits. Polycythaemia may occur in 10% of patients from tumour production of erythropoietin. They may also arise within the spinal cord causing radicular pain, posterior column loss and pyramidal involvement with weakness, spasticity and bladder disturbance. There may be an associated cavity within the cord and clinical syringomyelia. Rarely, haemangiomas arise supratentorially.

Haemangioblastomas are most commonly associated with VHL syndrome. This condition is caused by a germ line defect in a tumour suppressor gene on chromosome 3p25. VHL is associated with multiple haemangiomas which may be asymptomatic. There is also retinal angiomatosis, renal cell carcinoma, visceral cysts and phaeochromocytoma.

Haemangioblastomas are relatively sharply demarcated: invasion and remote metastases are rare. Surgical resection is generally possible and total resection curative. Residual or inoperable tumours may be treated with external beam radiotherapy or stereotactic radiosurgery. The overall outcome is good with 5-year survival of 75%, particularly with small tumours and complete surgical removal. Screening for VHL is necessary in all patients with haemangioblastoma.

Colloid cysts, Rathke's pouch tumours and neuro-enteric cysts

These benign cystic lesions represent developmental malformations. The cysts are lined by columnar, mucin-producing epithelial cells which resemble respiratory or enteric lining. Colloid cysts are characteristically located in the roof of the third ventricle and may block the foramen of Monro leading to obstructive hydrocephalus. Characteristically, this may be postural with intermittent headache and drop attacks. Rathke's pouch cysts arise in the sellar region. Neuro-enteric cysts arise in the spinal cord or within the brain. Imaging shows isodense or hypodense lesions on CT scan and MRI. Symptomatic lesions require surgical excision and a VP shunt may be necessary if there is hydrocephalus.

Neurofibromas and schwannomas

Schwannomas are tumours of Schwann cells and account for about 8% of primary intracranial tumours. Their most common location is in the cerebellopontine angle but they can occur on almost any cranial nerve, particularly the Vth and VIIth, as well as on spinal nerve roots and peripheral nerves. Bilateral vestibular schwannomas are the hallmark of neurofibromatosis Type 2 (NF2), caused by a mutation on chromosome 22 and inherited as an autosomal dominant disease. Typically, patients with NF2 present at a younger age than patients with sporadic tumours. In contrast, NF1 is associated with a mutation on chromosome 17, and presents with more peripheral tumours as well as optic pathway gliomas and spinal neurofibromas. These patients also have retinal disease with Lisch nodules, café-au-lait patches, subcutaneous schwannomas or neurofibromas and possibly further intracranial or intraspinal tumours, including gliomas and meningiomas.

Clinical features of vestibular schwannomas include dizziness and vertigo, which may be initially intermittent, and progressive unilateral hearing loss and tinnitus. Later symptoms arise from trigeminal nerve, facial nerve and brainstem compression causing facial sensory symptoms, facial twitching and weakness and ataxia of limbs and trunk. Hydrocephalus may occur at a late stage.

The management depends on the age of the patient, the size and growth rate of the tumour and the presence of other co-morbidity. Observation with 6- or 12-monthly MRI scans is appropriate for patients over the age of 70, particularly if hearing has been lost. The majority of patients will have active treatment and, in this respect, the pendulum has swung heavily away from surgical microdissection to stereotactic radiosurgery or fractionated stereotactic radiotherapy. This can be performed with either the multiple source cobalt unit (gamma knife, often used to deliver single fraction radiosurgery treatments) or a linear accelerator (LINAC) which can deliver single or multiple fraction radiotherapy using a relocatable frame system. Both are carried out in an out-patient setting without the need for a general anaesthetic. The goal is to deliver a high dose of radiation to the tumour volume with minimal doses to surrounding structures, i.e. cranial nerves, brainstem and vessels. This will slow down or stop the growth but does not cause the tumour to disappear. Single fraction radiosurgery can only be applied to tumours <3.5 cm in diameter. Tumour reduction occurs in 70–90% of cases although there is a temporary volume increase in about 25% of patients. Facial nerve damage occurs in about 10–15% but hearing is preserved (in small tumours) in more than 50% of cases. The main disadvantages of radiosurgery include its limitation to small tumours, the possibility of deteriorating cranial nerve function after treatment and potential risk of malignant change within the remaining schwannoma.

In contrast, microsurgical tumour resection offers the possibility of cure for any tumour and is the only treatment option for medium and large tumours. The risk of recurrence and mortality are both <1%. The main long-term complication is facial paralysis. Incomplete facial recovery occurs in about 20% of patients and there is a 5% rate of complete facial palsy, which may require facial nerve reconstruction.

Neurological complications of cancer

Neurological complications of cancer (NCC) are common, serious, potentially disabling and often treatable when correctly diagnosed. The most frequent complaints overall are pain, confusion, headache and weakness. NCC are common reasons for admission to hospital. Many oncologists have had little formal training in neurological assessment. Many neurologists see relatively few cancer patients and are unlikely to know in detail the recent advances in cancer management and the way in which the nervous system can be affected by them, especially neurotoxicity of recently introduced chemotherapy. Radiation treatment can lead to delayed neurological problems which may emerge years after the original treatment, possibly when the original cancer has been cured. It is thus essential that neurologists have a broad overview of NCC in order to focus on the differential diagnosis and appropriate tests. This will often be in liaison with an oncologist. Table 20.7 outlines the main neurological problems in cancer patients.

As with any neurological presentation, the history is key. With respect to patients with known cancer the following points should be ascertained: details of primary tumour, site and grade, presence of known metastases, treatment received to date and current drug treatment, for the cancer, for pain and any existing complications.

Direct effects

The majority of NCC are caused by direct invasion of the nervous system or metastatic spread. This is usually easily diagnosed

Table 20.7 Neurological complications of cancer.

Direct effects
Infiltration by primary tumour or draining lymph nodes: e.g.
  Nasopharyngeal carcinoma – multiple cranial nerve palsies
  Lung cancer, e.g. Pancoast tumour causing T1 radiculopathy
  Breast cancer – brachial plexus lesions

Metastases
Brain
Skull base and vault
Dura
Spinal cord – extradural, intradural, intramedullary
Leptomeninges (malignant meningitis)
Brachial and lumbar plexus
Perineural

Indirect effects
Metabolic encephalopathies, e.g. hyponatraemia due to SIADH
Vascular disorders, e.g. hypercoagulable states, haemorrhage and non-bacterial thrombotic endocarditis
CNS infections
Paraneoplastic neurological disorders

Unwanted effects of treatment
Chemotherapy neurotoxicity
Radiotherapy neurotoxicity
Intrathecal administration
Compression neuropathies, e.g. after surgery

SIADH, syndrome of inappropriate antidiuretic hormone.

clinically and/or with appropriate imaging. As the sensitivity of imaging increases, it has become evident that the highest resolution imaging is frequently needed to reach a diagnosis. MRI with contrast enhancement or positron emission tomography (PET) may well be necessary if less sophisticated imaging is negative. Although there are common patterns of tumour spread, e.g. bony metastases with breast, bronchus, prostate, kidney and thyroid cancer, almost any malignancy can spread anywhere within the neuraxis.

Infiltration

Invasion or compression of neurological structures occurs when a primary or secondary tumour or draining lymph node is in direct contact with a nerve, nerve root, spinal cord or brain. Tumour invasion of nerve roots is sometimes associated with severe pain: this may be helpful to differentiate malignant infiltration from effects of previous treatment. In some cases, e.g. Pancoast tumour, neurological symptoms may be the presenting complaint. Less commonly, microscopic growth of tumour cells, particularly lymphoma along nerve sheaths, occurs after the primary tumour has been treated. Common presentations of direct invasion include multiple cranial nerve palsies with nasopharyngeal carcinoma, brachial plexus lesions from breast cancer in the axillary tail, lung cancer causing a T1 root lesion with Horner's syndrome (Pancoast's syndrome) and in children paraganglioma and/or neuroblastoma causing spinal cord compression via paravertebral spread through the neural foramina into the epidural space.

Metastases

Metastases are a major cause of neurological problems in patients with cancer. They are commonly fatal when they involve the CNS. They occur in three ways: by haematogenous spread, the usual mechanism of brain metastases; lymphatic dissemination, usually to peripheral nerves; or by dissemination through the CSF producing leptomeningeal metastases. The likelihood of metastasis increases with increasing primary tumour size and the duration of patient survival following treatment to the primary site. The site to which a tumour metastasizes depends on the anatomy of the venous and lymphatic drainage of the organ harbouring the tumour, the micro-environment of the receiving organ and the molecular phenotype of the tumour, particularly the propensity to express surface adhesion molecules.

Malignant meningitis

Malignant meningitis (MM) is one of the most sinister complications of any cancer, occurring in 3–8% of patients often at the later stages of the disease but occasionally presenting in a patient with no known tumour. MM is becoming more frequent because of the improved prognosis of patients with systemic cancer and earlier diagnosis with MRI. It is characterized by invasion of the leptomeninges and/or CSF by cancer cells and can affect either brain or the cord. Tumours that commonly cause MM are lung and breast cancer, melanoma and leukaemia/lymphoma, where blood stream spread is the route into the CNS. However, almost any tumour can cause MM, including colorectal and urogenital cancer. MM occurs, if rarely, as a complication of primary brain tumours. This is seen in paediatric practice with medulloblastomas, ependymomas and oligodendrogliomas.

In adult practice, breast is the most common solid tumour associated with MM followed by lung cancer, both small cell and non-small cell. In some 5% of these cases, the patient presents *de novo* with MM. In some cases the primary may never be found. Although haematogenous invasion is the most common route for cancer cells to reach the leptomeninges, direct invasion from metastases in contact with the meninges, i.e dural, subdural and intraparenchymal metastases and perineural invasion occurs. Iatrogenic seeding during surgical resection of posterior fossa metastases has even been implicated in the pathogenesis of MM.

MM can present with cerebral, cranial nerve, spinal and/or radicular symptoms and signs (Table 20.8), either in isolation or as a multifocal process. Patients may have combinations of cranial nerve palsies, sensorineural deafness, papilloedema resulting from communicating hydrocephalus, seizures or patchy radiculopathy. Patients should be asked about numb patches in the body and examined for evidence of nerve root involvement.

Table 20.8 Clinical presentations of malignant meningitis.

Location in neuraxis	Symptoms	Signs
Cerebral	Headache, nausea and vomiting	Papilloedema
	Cognitive changes, impaired consciousness	Encephalopathy
	Gait problems	Hemiparesis, ataxia
	Seizures	
	Focal deficits	
Cranial nerves	Diplopia	III, IV, VI lesions
	Visual loss	Optic neuropathy
	Facial weakness/numbness	V, VII lesions
	Deafness/vertigo	Sensorineural hearing loss, nystagmus
	Dysphagia, dysarthria	IX, X, XII nerve lesions
Spinal cord and roots	Back/neck/radicular pain	Nuchal rigidity
	Weakness	LMN weakness, reflex asymmetry
	Patches of numbness	Dermatomal sensory loss
	Sphincter dysfunction	e.g. Urinary incontinence, constipation

LMN, lower motor neurone.

Gadolinium-enhanced MRI provides the most sensitive imaging modality. Abnormal enhancement with MRI is seen in 70% of MM patients, compared to about 30% with contrast-enhanced CT. Linear enhancement may be seen in cerebral sulci and within the ponto-medullary cisterns. This gives rise to a characteristic pattern of sugar coating, of the brainstem, within the cerebellar folia or along the spinal cord appearing as tramlines over the cord or nodular meningeal deposits. Communicating hydrocephalus occurs in 10% of patients. A meningitic syndrome is sometimes seen but not commonly. Many MM patients simply feel generally unwell. Imaging should always be carried out prior to lumbar puncture as the procedure itself may lead to artefactual meningeal enhancement. In contrast to its role in diagnosis, MRI is of little use for monitoring the response to therapy.

CSF examination with cytology of a large volume (at least 10 ml) of fluid is the single most useful investigation both for diagnosis and monitoring treatment. It is nearly always abnormal in patients with MM irrespective of the results of CSF cytology. Abnormalities include raised CSF protein (usually <2 g/dL except in cases of spinal block), low CSF : plasma glucose ratio and elevated CSF white count. There is little correlation between CSF white cell count and the likelihood of detecting malignant cells. Sensitivity of CSF cytology rises from 65% after one lumbar puncture to 90% after three punctures. Ideally, fluid should be taken to the cytology laboratory immediately after collection in order to minimize cell autolysis. Certain tumours, e.g. leukaemias, are more likely to shed cells into the CSF than others – in cytology negative cases flow cytometry using specific lymphoma markers may be helpful in suggesting the diagnosis. There is no benefit in measuring tumour markers within the CSF.

Treatment of MM is solely palliative. Thus, the decision to treat a patient with MM and metastatic disease depends on the patient's tumour status and their overall physical condition. In general, MM once diagnosed has a median survival of 2–6 months. Particularly poor prognostic factors include low performance status, presence of encephalopathy and melanoma/lung cancer/brain tumour as the primary. Patients with breast cancer and MM have a median survival of 7.5 months and are therefore more often eligible for aggressive treatment.

Corticosteroids, non-steroidal anti-inflammatory drugs and opiates form the basis of palliative treatment. Anticonvulsants may be needed. Cranio-spinal radiotherapy is rarely indicated because of significant morbidity associated with treatment, particularly myelosuppression and the time taken for planning and carrying out treatment. Radiotherapy is used for treatment of isolated sites of symptomatic bulky disease, particularly in the posterior fossa and spinal cord.

Drug therapy, when appropriate, consists of systemic and intrathecal chemotherapy and hormonal therapy, e.g. tamoxifen for breast cancer. Systemic chemotherapy is often ineffective because of difficulties in achieving significant levels of cytotoxic drug within the CSF. It is limited largely to treatment of chemosensitive tumours such as breast cancer and lymphoma.

Intrathecal chemotherapy via an Ommaya reservoir connected to the lateral ventricles or via repeated lumbar punctures is usually reserved for patients with good performance status and no or limited evidence of systemic disease. The most commonly used drugs are methotrexate and cytarabine, active against leukaemia and lymphoma, and methotrexate and thiotepa for breast cancer. Cytarabine is now available in a depot liposomal formulation which reduces the need for lumbar punctures from two per week to one every 2 weeks. None of these agents has intrinsic activity against melanoma and lung cancer. Novel agents that have been used intrathecally include topotecan and gemcitabine.

Table 20.9 Causes of toxic/metabolic encephalopathy with cancer.

Tumour	Brain or meningeal metastases
Drugs	Opioids, benzodiazepines, corticosteroids, chemotherapy
Infections	Pneumonia, UTI, intra-abdominal abscess, CNS infection
Hypoxia	Pneumonia, pulmonary emboli
Electrolytes	Hypercalcaemia, hyponatraemia, hypophosphataemia
Endocrine	Adrenal insufficiency, e.g. rapid steroid withdrawal
Hepato-renal	Uraemia, hepatic failure
Nutritional	Thiamine deficiency (Wernicke encephalopathy)
Unrelated	Alcohol or drug abuse or withdrawal, cardiac/respiratory co-morbidity

UTI, urinary tract infection.

Indirect effects

Toxic/metabolic encephalopathy

Toxic/metabolic encephalopathy is a frequent occurrence in cancer patients, particularly in the terminal phases, and presents when fully developed with delirium or an acute confusional state. There are numerous causes (Table 20.9). A thorough evaluation is required: many causes are reversible. The earliest manifestations are subtle deficits of concentration and attention which progress through towards inappropriate behaviour, cognitive disturbance and into a full-blown state of delirium, characterized by either a state of lethargy and apathy (quiet delirium) or by hyperactivity and restlessness, similar to that seen in the delirium tremens of alcohol withdrawal. These symptoms may be initially mistaken for anxiety and depression, particularly as neurological signs are often absent and rarely focal. The neurological examination reveals deficits in orientation, attention, concentration and language, short-term memory problems and visuo-spatial disorientation. Tremor, myoclonus and asterixis are also sometimes seen. Investigation of these patients consists of excluding a primary neurological cause such as brain metastases or MM and identifying any treatable extracerebral or metabolic condition. A careful drug history is mandatory.

Vascular disorders

Cerebrovascular problems are relatively common in cancer patients. They are brought about either by direct effects of a tumour and/or its treatment on blood vessels, or by a coagulopathy caused indirectly by the neoplasm. Cerebral haemorrhage can be the presenting symptom of a primary intracranial tumour or, more commonly, metastases, particularly from melanoma, extracranial germ cell tumours and rarely colonic carcinoma. The most common primary brain tumours associated with intratumoral haemorrhage are oligodendrogliomas, glioblastomas and germ cell tumours. Bleeding is also sometimes seen in meningiomas, medulloblastomas, choroid plexus papillomas and ependymomas.

Intracerebral haemorrhage can also follow thrombocytopaenia caused by either tumour or leukaemic invasion of bone marrow, chemotherapy or radiotherapy.

A hypercoagulable state leading to arterial or venous thrombosis is sometimes seen in patients with widespread metastatic disease caused by multiple pro-coagulant effects of cancer on platelet function and coagulation factors. This was first described in 1865 by Trousseau who noted accelerated clotting times and thrombo-phlebitis in more than 60% of the cancer patients he saw. Haemostatic abnormalities occur in more than 90% of cancer patients, most commonly presenting as deep vein thrombosis or disseminated intravascular coagulation (DIC) with depletion of platelets and clotting factors. In general, venous thrombo-embolism is more frequent in solid tumours while DIC causes both venous and arterial occlusions and is seen in widespread metastatic cancer and haematological malignancies. Occasionally, drug therapy causes abnormal coagulation, e.g. cerebral vein thrombosis associated with L-asparaginase in acute leukaemia. Rarer causes of cerebral infarction include tumour emboli (usually intracardiac tumours such as atrial myxoma), non-bacterial thrombotic endocarditis (NBTE) and cerebral vasculitis. A diffuse brain syndrome with multiple small infarcts can develop. Occlusion of venous sinuses may also result from compression or invasion by metastatic tumour, particularly breast cancer and lymphoma. Other causes of hypercoagulability include hyperfibrinogenaemia, seen in some 50% of cancer patients, and antiphospholipid syndrome.

Non-bacterial thrombotic endocarditis

This form of endocarditis, also known as marantic endocarditis, is a rare but well-recognized cause of ischaemic stroke in the cancer population, particularly patients with mucinous adenocarcinomas from the lung, pancreas, stomach and ovary. This condition is poorly understood. NBTE results from predisposition for platelets and fibrin plugs to deposit on cardiac valves, usually aortic and mitral, giving rise to sterile vegetations, which can cause arterial emboli. One-third of NBTE patients have a purely neurological presentation either with a diffuse encephalopathy, focal signs, including transient ischaemic attacks or rarely spinal cord infarction. Coagulation testing is usually normal although a few cases have evidence of DIC. In some cases, NBTE may precede the diagnosis of malignancy and can thus be the first presentation of an occult tumour. Treatment is directed to the underlying cause. Anticogulation is rarely helpful and carries substantial risks of haemorrhage.

CNS infections

Infections of the CNS occur more frequently in cancer patients than in the general population. They are one of the least common neurological complications of cancer and are almost always seen in patients with haematological malignancies. Nevertheless, they are important to keep in mind because these patients rarely have the florid symptoms and signs seen in immunocompetent patients. The most common presentation of CNS infection in a cancer patient is simply an altered mental state with headache and fever. Neck stiffness can be mild or absent. There should be a low threshold for imaging and lumbar puncture in such patients presenting with drowsiness and irritability. The causative organisms are different from those in the general population. In some 40% of patients multiple pathogens infect the CNS simultaneously. *Cryptococcus neoformans* and *Listeria monocytogenes* are the major causes of meningitis in cancer patients while enteric Gram-negative bacilli, *Toxoplasma gondii*, *Aspergillus fumigatus* and *Nocardia asteroides* are major causes of brain abscesses. Gram-negative organisms such as *Pseudomonas aeruginosa* and *Escherichia coli* are common causes of meningitis in neutropaenic patients: the paranasal sinuses should always be considered as possible sources of CNS infection, especially in these patients. Accurate microbiological diagnosis is essential in order to institute vigorous and appropriate antibiotic therapy. Despite this, treatment of CNS infections in this patient group is far less successful than in immunocompetent patients. There is a mortality of some 85% in neutropaenic patients with CNS infection. Survival depends on bone marrow recovery in addition to correct antibiotic treatment. Even when antibiotic treatment cures the infection, relapse and super-infection are common. The treatment of individual infections is discussed in Chapter 8.

Paraneoplastic neurological disorders

PND are uncommon neurological complications of cancer. They are important because they frequently present before the malignancy becomes symptomatic, because they cause severe neurological disability and because of the mechanism by which some forms of PND have been shown to cause disability is associated with specific antineuronal antibodies. Tumours can cause neurological symptoms through indirect mechanisms such as hyponatraemia and hypercalcaemia. However, the term paraneoplastic is usually reserved for disorders thought to be caused by autoimmune attack triggered by tumour antigens against nervous system components. Because PND are much less common than direct, metastatic and treatment-related complications of cancer, a neurological condition should only be regarded as paraneoplastic if a particular neoplasm associates with a remote but specific effect on the nervous system more frequently than would be expected by chance. For example, subacute cerebellar ataxia in the setting of ovarian cancer is sufficiently characteristic to be called paraneoplastic cerebellar degeneration (PCD), so long as other causes have been excluded. Conversely, carpal tunnel syndrome in a cancer patient is not paraneoplastic because both conditions, being reasonably common, are likely to coexist.

Incidence and prevalence

The precise incidence and prevalence of PND in the overall cancer population remains largely unknown. Certain common cancers that frequently associate with PND, e.g. SCLC, have been investigated extensively, but the majority of studies tend to concentrate on specific antineuronal antibodies and their neurological and tumour associations rather than provide prospective data on PND frequency.

The incidence of PND depends on the stringency of criteria used. In one early systematic study of PND, the term carcinomatous neuromyopathy was used to describe cancer patients with a combination of neuromuscular abnormalities, usually proximal muscle weakness, ataxia and distal sensory loss. Some 4% of women with breast cancer, 7% of patients with all cancers and 16% of men with lung cancer had evidence of PND compared with <2% of age-matched controls. The most frequent PND is Lambert–Eaton myasthenic syndrome (LEMS): this occurs in 2–3% of patients with SCLC. Overall, PND affect less than 1% of all patients with cancer. Cerebellar degeneration with ovarian cancer is the next most common form of PND occurring in about 1% of cases.

In patients without known cancer, the more common causes of neurological problems such as inflammatory and/or autoimmune conditions and hitherto undiagnosed tumours or metastases should be excluded before concluding that a patient is likely to have a PND.

The median age of onset of PND is over 60 years. Less than 10% of cases are in those under 50. PND occur relatively rarely in young people – except with the typical tumours of the 20–40 age group – Hodgkin's disease (PCD), testicular cancer (brainstem and limbic encephalitis), breast cancer (many different syndromes) and in children, neuroblastoma (opsoclonus-myoclonus).

The sex ratio of patients with PND is variable and probably depends on the underlying syndrome. In most studies there is a female preponderance of around 3 : 1 which cannot be accounted for by association with breast and ovarian gynaecological cancer alone.

Detailed long-term observational data for PND are not available. Response to treatment is frequently disappointing but LEMS may respond well. Spontaneous resolution of PND has occasionally been reported. PND cause serious disability. Most patients who do not succumb to either the neurological syndrome or the underlying tumour usually remain dependent on their carers.

Clinical features of predominantly CNS PND

PND are summarized in an anatomical classification in Table 20.10. Some CNS syndromes such as cerebellar degeneration are typically focal at presentation but frequently progress to involve other anatomical structures. Other PND are characterized by patterns of widespread dysfunction early on, e.g. the combination of limbic encephalitis of the medial temporal lobes and projections with a sensory neuropathy affecting dorsal root ganglia.

As more antibodies are recognized, the range of PND phenotypes is ever widening. Atypical forms, e.g. parkinsonism and other movement disorders are being reported increasingly.

PND usually begin abruptly and present within days to weeks, progressing rapidly. Stroke-like presentations are seen; imaging is usually negative. Occasionally, PND start gradually and progress slowly. Most patients become significantly disabled within a few weeks of onset and then plateau. Urgent investigation is indicated, especially in CNS syndromes, so that tumour therapy is started early to prevent progressive neuronal death and irreversible disability.

Table 20.10 Classification of paraneoplastic neurological disorders.

Site	Syndrome	Typical primary tumours
Brain	Cerebellar degeneration	SCLC, breast, ovarian, Hodgkin's disease
Brain	Limbic encephalitis	SCLC
Brainstem	Brainstem encephalitis	SCLC, testicular tumours
Brain and cord	Encephalomyelitis with rigidity	Breast, SCLC
Brain	Opsoclonus-myoclonus	SCLC, neuroblastoma, breast
Retina	Retinopathy	SCLC
Cord	Necrotizing myelopathy	Any
Cord and anterior horn cells	Motor neurone syndromes	Any
Dorsal root ganglia	Sensory neuronopathy	SCLC
Motor neurones	Subacute motor neuronopathy	Non-Hodgkin's lymphoma
Peripheral nerves	Vasculitic neuropathy	B-cell lymphoma
Peripheral nerves and roots	Acute inflammatory demyelinating polyradiculoneuropathy (as Guillain–Barré syndrome)	Hodgkin's disease
Peripheral nerves	Sensory/sensorimotor neuropathy	Any
Peripheral nerves	Mononeuritis multiplex	Any
Autonomic system	Autonomic neuropathy	SCLC
Peripheral nerves	Neuromyotonia	SCLC
Gut	Neurogastrointestinal enteropathy	SCLC
Neuromuscular junction	Lambert–Eaton myasthenic syndrome	SCLC
Neuromuscular junction	Myasthenia gravis	Thymoma
Muscle	Polymyositis and dermatomyositis	Any
Muscle	Acute necrotizing myopathy	Any

SCLC, small cell lung cancer.

Paraneoplastic cerebellar degeneration

PCD typically presents with the subacute onset of disequilibrium with increasing ataxia of gait, trunk and limbs. Complex eye movement abnormalities are seen with combinations of disordered pursuit movements, multi-directional nystagmus (often down-beating) and gaze palsies. Dysphagia and dysarthria develop. Severe disability develops rapidly. The condition usually stabilizes within 6 months although PCD sometimes evolves into a multi-focal neurological degeneration particularly in patients with anti-Hu antibodies. PCD occurs in a variety of tumours, most commonly ovarian and breast cancer, lung cancer and Hodgkin's disease. Tumours, if not previously diagnosed usually appear within weeks to months of the onset of symptoms, although there may be a lead-time bias because of the neurological diagnosis prompting a search for an underlying tumour.

Long intervals between PCD and tumour appearance are sometimes seen, e.g. PCD with characteristic clinical features and high titre anti-Yo antibodies has been diagnosed 13 years before breast cancer became evident.

Occasionally, PCD occurs after tumour diagnosis and treatment and in the case of Hodgkin's disease may be a harbinger of relapse.

A diagnosis of PCD is usually suspected when imaging of the posterior fossa is unremarkable in the presence of severe cerebellar ataxia. Unusual imaging abnormalities include diffuse oedema of the cerebellum and very early cerebellar atrophy. In PCD the cerebellum gradually becomes atrophic, over months. Other investigations, e.g. CSF examination, are rarely helpful but are useful to rule out leptomeningeal metastases which can occasionally cause isolated gait ataxia. CSF oligoclonal bands are usually positive in PCD.

The diagnosis of PCD is usually supported by finding antineuronal antibodies, specifically anti-Yo (38%), anti-Hu (32%), anti-Tr (14%), anti-Ri (12%) and anti-mGluR (4%). In one study of PCD, the functional outcome was better with anti-Ri and anti-Tr and worse with anti-Yo and anti-Hu. Patients receiving antitumour treatment (with or without immunosuppressive therapy) lived significantly longer than those who were untreated.

Pathologically there is severe and sometimes complete loss of cerebellar Purkinje cells with relatively minor thinning of the molecular layer. The deep cerebellar nuclei are spared except in cases of encephalomyelitis, when extensive inflammatory changes are seen.

Paraneoplastic encephalomyelitis and limbic encephalitis

Paraneoplastic encephalomyelitis (PEM) syndromes are one of the more common PND affecting the CNS and characterized by multi-focal inflammatory processes with predilection for limbic and brainstem structures. This process may occur with or without sensory neuropathy, autonomic neuropathy and LEMS.

Limbic encephalitis is usually seen in association with SCLC and presents with personality changes, irritability, depression, seizures, memory loss and sometimes dementia. The main finding on examination is severe impairment of episodic memory. This can improve dramatically with treatment of the underlying tumour. Investigations are usually non-specific – CSF may be inflammatory with pleocytosis and an elevated protein concentration. MRI may show high signal change within one or both medial temporal lobes. Epileptic discharges may be seen on EEG. Pathological changes affecting limbic and basal ganglia structures include neuronal cell loss, reactive microglial proliferation and peri-vascular lymphocytic infiltration. Commonly associated tumours are lung cancer (approximately 50%), testicular cancer (approximately 20%) and breast cancer (approximately 10%). Neurological symptoms precede cancer diagnosis in around half of cases by several months.

In one series over half of limbic encephalitis patients had antineuronal antibodies – anti-Hu, anti-Ta and anti-Ma. Anti-Hu antibodies usually associated with SCLC patients, multi-focal neurological symptoms and a poor outcome.

Patients with anti-Ta (anti-Ma2) antibodies tend to be young men with testicular tumours, hypothalamic involvement and a poor outcome. In patients with neither anti-Hu nor anti-Ta antibodies, lung cancer remains the most common tumour.

Reversible limbic encephalitis with dramatic neuropsychiatric presentation and ovarian teratoma has been recently described in association with antibodies against NMDA receptors.

The main differential diagnosis of limbic encephalitis is herpes simplex encephalitis although this is usually a more acute illness. Rarely, patients who have had bone marrow transplantation may develop a limbic encephalitis as a result of reactivation of human herpes virus-6.

Brainstem encephalitis

Brainstem encephalitis accounts for some 15% of cases of PEM. The clinical syndrome is characterized by brainstem dysfunction, cranial nerve palsies, long tract signs and cerebellar ataxia. Less common features include movement disorders such as parkinsonism, chorea, jaw-opening dystonia and myoclonus, the latter sometimes seen in association with anti-CV2 antibodies. Occasionally, brainstem encephalitis can cause central alveolar hypoventilation with recurrent respiratory failure or coma. As with limbic encephalitis, imaging and CSF examination are usually non-specific. The diagnosis is usually confirmed by finding antineuronal antibodies. An important differential diagnosis is *Listeria monocytogenes* rhombencephalitis.

Paraneoplastic encephalomyelitis with rigidity

This rare syndrome causes truncal and limb rigidity, stimulus-sensitive myoclonus, painful spasms and brainstem and spinal cord inflammatory involvement. It is usually fatal.

By contrast, the typical (non-paraneoplastic) stiff person syndrome with anti-GAD antibodies (see Chapter 5), characterized by axial and proximal lower limb stiffness, spasms with continuous motor unit activity on EMG behaves in a more indolent fashion. However, typical stiff person syndrome may rarely be a presenting feature of breast cancer and associated with anti-amphiphysin antibodies.

Paraneoplastic opsoclonus-myoclonus

Paraneoplastic opsoclonus-myoclonus (POM) is a rare syndrome seen typically in young children with neuroblastoma (dancing eyes syndrome) but also in adults with breast cancer and SCLC. Dramatic, chaotic, saccadic, multi-directional eye movements (opsoclonus) are associated with myoclonus of the trunk, limbs and head including the diaphragm and palate. There is also cerebellar ataxia. This syndrome is associated with cancer in about 20% of adults. It can also be seen in viral infections, drug overdose and as part of a post-infective encephalitis. As with other PND affecting the CNS, routine investigations are usually normal or non-specifically abnormal. Several autoantibodies have been described in POM, particularly anti-Ri (breast, SCLC) and anti-neurofilament antibodies in children with neuroblastoma.

Paraneoplastic retinal degeneration

PND can cause visual failure. Retinal photoreceptors, rods, cones and optic nerves can all be affected. Paraneoplastic retinal degeneration, otherwise known as cancer-associated retinopathy, is usually seen in SCLC and gynaecological tumours and associated with antibodies against recoverin, a photoreceptor protein. Visual loss is painless, bilateral and presents with loss of colour vision, night blindness and initial photosensitivity. There is loss of visual acuity. Field testing shows peripheral and ring scotomas. There may be arteriolar narrowing and mottling of the fundus caused by changes in the retinal pigment epithelium.

Necrotizing myelopathy

Necrotizing myelopathy is characterized pathologically by extensive necrosis of both white and grey matter, most marked in the thoracic segments. It is a rare cause of irreversible paraplegia.

Motor neurone syndromes

There is controversy whether typical motor neurone disease (MND) can be regarded as a true paraneoplastic syndrome. However, motor neurone syndromes are seen in three distinct groups of cancer patients. The first is a rapidly progressive MND-like condition with anti-Hu antibodies. The second is primary lateral sclerosis with breast cancer, lymphoma and myeloma. The third is typical MND developing some years after a diagnosis of cancer. It seems likely that the first two groups are indeed paraneoplastic: the third is probably not, reflecting the occurrence of two reasonably common diseases in the same patient.

Paraneoplastic sensory neuronopathy

Also known as dorsal root ganglionitis, paraneoplastic sensory neuropathy (PSN) causes subacute, rapidly progessive asymmetric and painful sensory symptoms dominated by severe proprioceptive loss, which affects upper limbs more than lower limbs. All sensory modalities are affected. In contrast, motor function is preserved. Nerve conduction studies show absent sensory action potentials but normal motor velocities. The CSF is typically inflammatory, particularly if the neuropathy is associated with encephalomyelitis. The differential diagnosis includes Sjögren's syndrome and cisplatin toxicity. The pathology centres on dorsal root ganglia where there are lymphocytic infiltrates and loss of ganglion cells.

Clinical features of predominantly peripheral PND

The peripheral nervous system is more commonly involved by PND than the CNS. Distal, predominantly sensory neuropathies are seen frequently in cancer patients and are more commonly caused by metabolic, nutritional and treatment-related axonal degeneration than paraneoplastic disease. However, in any patient presenting with a severe peripheral, predominantly sensory neuropathy in whom standard investigations are negative, about 10% will eventually be diagnosed with cancer, particularly if there is rapid progression to severe disability and absence of regeneration in a sural nerve biopsy (see Chapter 9).

Paraneoplastic neuropathies are clinical and immunologically heterogeneous and are associated with antineuronal antibodies in over 50% of cases. Anti-Hu antibodies are the most frequently identified. Patients with sensorimotor neuropathies also tend to have anti-CV2 antibodies in association with SCLC or high-titre antinuclear antibodies (ANA) in association with breast cancer.

Sensory and sensorimotor neuropathy

Paraneoplastic sensory and sensorimotor neuropathy is well recognized in many different cancers. Nerve conduction studies typically show a mixed sensory and motor axonal neuropathy. An occasional case may have typical demyelinating features and respond to intravenous immunoglobulin. Patients with an apparent chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with atypical features including resistance to first line treatments, an unusually aggressive course or the presence of myopathy and long tract signs should be investigated for an underlying cancer. The CSF is usually acellular in contrast with sensory neuropathy but the protein is usually raised. The unusual osteosclerotic form of myeloma can cause the combination of endocrine, dermatological and neurological features encapsulated within the acronym POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes). This neuropathy is typically demyelinating.

Acute inflammatory demyelinating polyradiculoneuropathy

Motor neuropathies are much less common than sensory neuropathies in paraneoplastic neurological disease. However, Hodgkin's disease patients can present with acute inflammatory demyelinating polyradiculoneuropathy (AIDP), a syndrome clinically and electrophysiologically indistinguishable from Guillain–Barré syndrome. Similarly, neuralgic amyotrophy (brachial plexitis) occasionally occurs in association with lymphoma, but a true paraneoplastic association is uncertain. Focal monomelic motor neuropathy has also been described.

Motor neuropathy

A subacute lower motor neuropathy is occasionally seen with non-Hodgkin's lymphoma presenting as a slowly progressive lower motor neurone syndrome affecting the lower limbs.

Vasculitic neuropathy

Vasculitis is occasionally associated with haematological malignancies and usually presents with rashes. Paraneoplastic vasculitic neuropathy has been described in patients with high-grade B-cell lymphoma.

Autonomic neuropathy

Paraneoplastic autonomic neuropathies are rare and present subacutely with gastrointestinal pseudo-obstruction, bladder dysfunction, orthostatic hypotension, labile blood pressure, pupillary abnormalities and pseudomotor dysfunction, impotence and xerophthalmia. Autonomic neuropathy can be the sole manifestation of an anti-Hu syndrome or part of a more widespread encephalomyelitis. In recent series of patients with anti-Hu antibodies, autonomic dysfunction was present in some 25% of cases and was the predominant symptom in approximately 5%.

Neuromyotonia

Neuromyotonia is a rare PND described with thymomas or SCLC. Muscle cramps, stiffness, twitching, sweating and abnormal relaxation after voluntary contraction occur. This is caused by hyperexcitability of peripheral nerve fibres. Electromyography shows abnormal doublet and triplet discharges with high intraburst frequency as well as myokymic and neuromyotonic discharges. Fasciculations and fibrillation potentials are common.

Acquired neuromyotonia typically is not paraneoplastic but an immune-mediated disorder (Isaac's or Isaac–Mertens syndrome) with elevated antibody levels against presynaptic, voltage gated potassium channels. These antibodies may also be detected in the even rarer Morvan's syndrome, also non-paraneoplastic, characterized by neuromyotonia, hyperhidrosis and features resembling limbic encephalitis.

Lambert–Eaton myasthenic syndrome

LEMS (see also Chapter 9) is caused by SCLC in 60% of cases and is characterized by proximal weakness, predominantly affecting lower limbs in association with autonomic disturbance such as impotence, constipation and dry mouth. The paraneoplastic syndrome is usually more severe than the autoimmune form but is electrophysiologically indistinguishable. The characteristic finding, consistent with presynaptic neuromuscular dysfunction and impaired quantal release of neurotransmitter, is of small compound muscle action potentials that decrement at low-frequency stimulation but increment at high-frequency stimulation. The diagnosis of LEMS is confirmed by finding antibodies against P/Q type voltage gated calcium channels (VGCC). Some patients with LEMS also have a cerebellar syndrome – and some patients with cerebellar syndromes but without LEMS have anti-VGCC antibodies.

Myasthenia gravis

Myasthenis gravis (MG) is the prototypical autoimmune disease with antibodies to post-synaptic acetylcholine receptors at the neuromuscular junction. In some 10% of MG cases there is an underlying thymoma. MG can thus be considered a paraneoplastic condition. No other tumour is associated with MG.

Polymyositis and dermatomyositis

Polymyositis or dermatomyositis can be paraneoplastic conditions. In general, patients with paraneoplastic myositis are older and have a more severe course than their autoimmune counterparts. Dermatomyositis in the elderly is much more likely to be paraneoplastic than polymyositis in the same age group.

Acute necrotizing myopathy

Acute necrotizing myopathy is rare. It is proximal, rapidly progressive, associated with rhabdomyolysis and usually fatal.

Diagnosis of PND

Diagnostic criteria for PND

Frequently, a PND will be suspected from the clinical features. Some guidelines for diagnosis are outlined below. Their aim is to facilitate diagnosis, classification and collaborative research. They rely upon finding a possible typical paraneoplastic syndrome and usually well-characterized paraneoplastic autoantibodies. A pattern of symptoms and signs can be diagnosed as possibly or definitely paraneoplastic using a descending hierarchy:

1 Presence or absence of known cancer;
2 Presence or absence of a well-described syndrome;
3 Presence or absence of well-characterized antineuronal antibodies; and
4 Exclusion of other causes of a similar neurological syndrome, particularly malignant meningitis.

Paraneoplastic antineuronal autoantibodies

The detection of serum paraneoplastic antineuronal autoantibodies (PNA) is highly specific and forms the cornerstone of diagnosis of PND. Sensitivity varies between different syndromes. At best it is only 80–90% and therefore a diagnosis of PND cannot be excluded if PNA testing is negative. Table 20.11 shows the more common antineuronal antibodies, their clinical associations, immunohistochemical staining patterns and putative antigens. There is a bewildering array of PNA. It is therefore reassuring that a detailed knowledge of specific antibodies is rarely required as most laboratories test patients sera against crude homogenates of CNS tissue (usually rat or mouse) both by immunohistochemisty and Western immunoblotting. Further characterization of the specific antigen can then be carried out using recombinant proteins.

Table 20.11 Paraneoplastic antineuronal antibodies and their clinical and immunological associations.

Antibody	Neurological syndrome	Immunohistochemistry	Western Blot	Antigen	Associated tumour
Hu (ANNA 1)	PEM/PSN, LE, PCD, LEMS, intestinal neuropathy	Neuronal nuclei in CNS and PNS	36–40 kD	Hu family triplet bands	SCLC, neuroblastoma, non-SCLC, prostate
Ri (ANNA 2)	POM, PEM, PCD	Neuronal nuclei in CNS	55 & 80 kD	Nova 1 & 2	Breast, SCLC, gynaecological
Yo (PCA 1)	PCD	Purkinje cell cytoplasm	34 & 62 kD	Cdr 1 & 2	Breast, ovary, uterus
Tr	PCD	Purkinje cell cytoplasm (molecular layer)	No reactive protein	Unknown	Hodgkin’s disease
Amphiphysin	Stiff person syndrome, rapidly progressive myelopathy	Synaptosomes	128 kD	Amphiphysin	Breast, SCLC
CV2/CRMP5	PEM, chorea, uveitis, optic neuropathy, intestinal neuropathy	Diffuse neuropil, cytoplasm of oligodendrocytes	66 kD	CRMP-5	SCLC, breast, thymoma
Ma	PEM, PCD, BE	Nuclei and cytoplasm	37 kD		Miscellaneous
Ta (Ma2)	BE, LE, hypothalamic syndrome	Nucleolus, perikaryon	40 kD	Ma 2	Testicular cancer
mGluR1	PCD	Membrane glutamate receptors		mGluR1	Hodgkin’s disease
AGNA	LEMS	Glial nuclei in cerebellum		SOX1	SCLC
NMDA receptor	LE with prominent neuropsychiatric features, autonomic dysfunction, movement disorder	Hippocampal neuropil		NR1/NR2 heteromers	Ovarian teratoma

BE, brainstem encephalitis; LE, limbic encephalitis; LEMS, Lambert–Eaton myasthenic syndrome; PCD, paraneoplastic cerebellar degeneration; PEM, paraneoplastic encephalomyelitis; POM, paraneoplastic opsoclonus/myoclonus; PSN, paraneoplastic sensory neuronopathy.

Imaging in PND

There is no imaging modality that can identify a PND with a high degree of sensitivity and specificity. The role of MRI is predominantly to rule out structural disease. Imaging is used for detection of an underlying tumour. Whole body FDG-PET scanning is useful when conventional imaging is unremarkable or equivocal as it detects small (6–8 mm) tumours if metabolically active.

Treatments for PND

The treatment of PND is unsatisfactory. Early detection and treatment of the tumour seems to offer the greatest chance of stabilization of PND. By contrast, immune-modulating therapies aimed at reducing levels of circulating antineuronal antibodies, e.g. plasma exchange, intravenous immunoglobulin, steroids and immunosuppressants, usually have no or modest effects on CNS syndromes, although they be helpful in LEMS (Chapter 9). Palliative symptom-directed therapy is usually the most appropriate management.

Neurological complications of chemotherapy

Many chemotherapeutic drugs are neurotoxic, causing particularly neuropathy and encephalopathy (Table 20.12). In many instances, diagnosis of treatment-induced disease is based on clinical experience and exclusion of other causes. Frequently, combination therapy causes previously unrecognized syndromes as some drugs act synergistically with others and with radiotherapy. Neurotoxicity from cancer chemotherapy tends to be frequent and severe in patients with pre-existing neurological disease.

Polyneuropathy

A pure sensory neuropathy, often painful, is most commonly associated with Vinca alkaloids, taxol and cisplatin. Motor neuropathies are rare but are occasionally seen with suramin and vincristine. They are usually reversible on cessation of the drug.

Encephalopathy

Almost any cancer chemotherapy can cause an acute encephalopathy characterized by seizures and confusion. The most notable example is the combination of methotrexate and cranial irradiation causing an irreversible leucoencephalopathy (Figure 20.17).

Table 20.12 Chemotherapy-related neurotoxicity.

Acute encephalopathy	Methotrexate, cisplatin, vincristine, asparaginase, ifosfamide
Chronic encephalopathy	Methotrexate, 5-fluorouracil/levamisole
Cerebellar syndrome	5-fluorouracil, cytosine arabinoside, ciclosporin, vincristine
Visual loss	Tamoxifen (retinopathy), cisplatin (cortical blindness)
Deafness	Cisplatin
Myelopathy/aseptic meningitis	Intrathecal methotrexate, cytosine arabinoside
Neuropathy	Vinca alkaloids, cisplatin, oxaliplatin, taxol

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Support services

A variety of support services exist and some of these are listed below.

British Brain and Spine Foundation (telephone: 0808 808 1000; www.bbsf.org.uk)

Cancer Research UK (telephone: 0800 226 237; www.cancerhelp.org.uk)

International Brain Tumour Alliance (www.theibta.org).

Macmillan Cancer Relief (telephone: 0808 808202; www.macmillan.org.uk)

Samantha Dickson Brain Tumour Trust (telephone: 0845 1309733; www.braintumourtrust.co.uk)

21

Psychiatry and Neurology

Michael Trimble

Liaison neuropsychiatry

During the last 25 years there have been numerous changes in psychiatric practice. Of note, there has been expansion of liaison psychiatric units in general hospitals, treating both in-patients and out-patients. Liaison practice has also flourished within specialist neurological units, reflecting the needs of the patient communities, their ethnicity and prevalent patterns of neurological illness.

While this chapter reflects the way in which practice has developed at the National Hospital, it is of general relevance to practical neuropsychiatry – and to the problems encountered by neurologists and liaison psychiatrists worldwide.

Requests for neuropsychiatric consultations often reflect diagnostic difficulties, e.g. trying to evaluate the meaning of neurological signs and symptoms that cannot be equated with an understanding of neuropathology. Other requests follow a breakdown of patient–physician relationships, or sometimes discord among staff members because of differing views about the patient's management. Thus, in many settings, it is not the severity of the patient's psychopathology that leads to referral, but anxiety within the group of people looking after the patient. The latter can even be exploited by patients.

Another reason for referral is behaviour that has become difficult to manage on a neurological ward. For example, aggressive behaviour can easily arise in patients with neurological illnesses on account of their cerebral impairment. Infrequently but importantly, patients are admitted to hospital and then are found to have suicidal ideation. A key function of psychiatric liaison assessments in such settings is to evaluate the potential risk.

In practice, liaison psychiatric consultation requires assessment of the patient's mental state and evaluation of their behavioural problems in relationship to knowledge of their past and present medical and neurological history, but importantly also their psychosocial status. Especially relevant is the need to eke out information of the social settings in which the patient is embedded. This may reveal inescapable conflicts, financial embarrassments, losses and bereavements which may lead understandably to stress and psychiatric disorders such as anxiety or depression. Much of the skill of liaison neuropsychiatry is to put such information into the context of presentations, signs and symptoms of neurological disease.

An opinion, when formulated, needs to be communicated to the patient and neurological team in language free from jargon. This will follow from diagnostic formulation through to suggestions for management. Specific recommendations sometimes involve the use of psychotropic drugs and suggestions to nursing staff about how to manage patients with challenging behaviours. Recommendations for additional nursing staff and the level and type of observation required are often important.

Figures vary, but it is estimated that at least up to 50% of patients admitted to neurological units have a recognizable psychiatric disorder and an additional number are admitted who have more straightforward cognitive impairments. It is also acknowledged that in over half of these admissions, cognitive and neuropsychiatric abnormalities remain undiagnosed at patient discharge, although the diagnoses may well be very relevant in terms of symptom resolution and potentially helpful in the next stage of patient referral and for the general practitioner.

Estimates of the primary psychiatric disorders in such neurological populations reveal that the majority are affective or personality disorders. About 20% of neurology patients have affective disorders (e.g. depression or bipolar disorder). A much smaller percentage (2–3%) are psychotic. In a neurological setting, pain is an extremely frequently reported psychiatric symptom. Headache, dizziness, body pain and difficulties with attention and concentration are also common psychiatric symptoms that occur in a neurological setting. These can easily be mistaken for symptoms of an organic neurological disorder. It is on account of such somatic symptoms that many patients with minor psychopathology are

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Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

seen in neurological out-patient clinics and it is of relevance that many neurologists choose psychotropic drugs in their management both in in-patient and out-patient settings. In a neurological setting, depression is the most common treatable diagnosis in patients who often present with cognitive or somatic symptoms. In addition, depression can coexist with neurological disease, either because of the patient's worry at having some disorder they fear and do not understand, or because the function of the brain itself is altered, leading directly to the symptoms. Thus, many neurological diseases, being chronic and disabling, lead patients into secondary depression that not only complicates and magnifies reporting of neurological symptoms, but also when unrecognized leads on to multiple unwarranted investigations, increasing stress, worry and symptoms themselves.

In a subsection of patients, the diagnostic problem is to differentiate between acute organic brain syndromes (e.g. delirium or a cerebral signature syndrome such as apraxia or aphasia) and primary psychiatric disorders such as schizophrenia. Other examples are unravelling the causes of catatonia and the evaluation of patients on ITU with pseudocomas or non-epileptic seizures.

The close association between neurological and psychiatric disorders is one of the more important reasons why the training of neurologists needs to incorporate psychiatry and to reflect the importance of neuropsychiatry. In order to evaluate patients properly it is important not only to have good working knowledge of presenting signs and symptoms and prognosis of neurological diseases, but also those of psychiatric illness. If this does not occur, patients with relatively straightforward psychiatric problems can be subjected not only to a multitude of unnecessary, costly and expensive investigations, but also receive diagnoses that are incorrect. This can lead the patient on a somatic medical pilgrimage which can continue for many years. This can restrict their lifestyle (e.g. the incorrect diagnosis of epilepsy and loss of a driving licence) but also leads to a diminished quality of life – when the fallacious neurological diagnosis causes unemployment and an unnecessarily gloomy prognosis.

Medically unexplained symptoms

A common request for neuropsychiatric assessment arises when a patient has symptoms (usually neurological) that are unexplained. The range of such symptoms runs the gamut of any neurological textbook. Patients may present with monosymptomatic problems (e.g. loss of the use of an arm, or blindness) to polysymptomatic presentations, with multiple symptoms in multiple body systems.

The older term for this was hysteria and patients were referred to as having conversion disorders. Newer classifications (much of psychiatry is now driven by diagnostic categories within both the ICD-10 and the DSM-IV-TR) refer to this as somatoform disorder.

Somatization relates to a process whereby patients express mental states as somatic symptoms by mechanisms usually unrevealed, but sometimes transparent if carefully sought. A more appropriate definition of somatization is that it is, 'a process by which the body (the soma) is used for psychological purposes or for personal gain. Any one symptom or constellation of symptoms may concurrently serve more than one function, including issues related to intra-psychic conflicts, interpersonal relationships and social or environmental problems.'

It is well accepted that symptoms of somatization are recognized more commonly in females than in males, that they often include pain-related symptoms and may be associated with acute psychological distress. It is known that there is a close relationship between grief and bereavement and the subsequent reporting of somatic symptoms. It is surprising how often the possibility of bereavement or substantial loss of some kind in relationship to the presentation is missed in the history.

As a generality, patients with somatoform disorders fall broadly into two categories. First, there are those with symptoms of relatively acute onset, limited in number and that resolve reasonably quickly. Underlying this may well be an anxiety disorder (e.g. following stress or as part of a post-traumatic stress disorder) or an underlying depressive illness. These problems resolve with the passage of time, as long as appropriate psychological and psychiatric interventions are instigated, including sometimes brief cognitive–behaviour therapy, psychotherapy and psychotropic drugs.

The second form of somatoform disorder, extremely important in neurological practice, is somatization disorder. This represents a much more complex and serious problem. In general, patients are polysymptomatic. Recent DSM-IV-TR diagnostic criteria require that patients present with multiple medically unexplained symptoms over time that cause significant social and occupational impairments, usually before the age of 30. Patients often describe their symptoms in colourful and theatrical terms but are also noted to be inconsistent historians. The latter is of considerable importance. Thus, not only are the symptoms of which they complain often difficult to clarify, but if in addition the history of their complaint and medical background is uncertain, the diagnostic confusion becomes the greater. Often such patients will have a history of an obvious conversion disorder previously, although this will have been certified medically by using such terms as irritable bowel syndrome, rheumatoid arthritis, possible lupus, asthma, post-viral fatigue or fibromyalgia. These diagnoses can have, to say the least, very imprecise boundaries. Nonetheless, one of the most important aspects to diagnosis is the past medical history, which will reveal a propensity for medical importuning and a tenacity to such diagnostic labels as those above, accompanied by a salmagundi of medications rarely surrendered without a struggle.

The suggestion that such patients have some kind of uniform personality style, the hysterical personality, has not stood the test of time. However, the language that they use, their interactions and responses to their medical carers and advising physicians are often notable and consistent. This has led to the development of the concept of abnormal illness behaviour. This evolved from the social sciences and the term 'illness behaviour', which essentially describes the way in which patients monitor their bodies, interpret any symptoms they have and take remedial actions to utilize health care they feel appropriate. There is considerable social variability of behaviours relating to illness and this is entwined within the different perspectives that patients and doctors have upon presenting complaints. Thus, which patient is treated by which specialist is to some extent culturally and socially determined. This is why conceptual distinctions between symptoms and signs, but also between syndromes, diseases and illnesses need to be clearly made. Thus, patients present to doctors with their illnesses within which are embedded syndromes that are clinically diagnosed based upon observations (signs) and complaints (symptoms), but they do not present with diseases *per se*. There is a huge chasm between some pathologically identified altered state of tissue and patients' complaints.

Abnormal illness behaviour has been defined as the persistence of an inappropriate or maladaptive mode of experiencing, evaluating or acting in relation to one's own state of health. It is revealed by a patient's way of behaving and responding to symptoms and by their interactions with physicians and others. The resoluteness with which these patients hold on to their symptomatology, their obstinate somatically based beliefs about the cause of symptoms and inability to accept a potential psychological exploration and explanation is reflective of their abnormal illness behaviour. A breakdown of physician–patient interaction is typical in such a setting, in which the response of the patient to test results (normal) or diagnostic possibilities (non-neurological) is with indignation and then rejection. As the ability of both sides to manoeuvre the situation narrows, the patient is discharged from care or discharges him/herself.

It is therefore most important if a patient is being evaluated for symptoms that appear to be, or may be, medically unexplainable for the neurologist to include in the initial discussion with the patient that amongst those who may be examining them there is likely to be a member of a liaison neuropsychiatric team. In addition to physical investigations, psychological ones will be part of their work-up. There is nothing more disarming for a neuropsychiatrist to see a patient who has been told 'there is nothing we can find the matter with you, therefore we're calling in the psychiatrist'. Both are setting off on the wrong foot.

In such settings, full understanding of the patient's symptoms requires an elaborate assessment of personality, past illness behaviour history, the present mental state and the patient's current environmental and interpersonal stresses. In theory, this should not require two separate evaluations. Relevant data should be obtained in a single interview and indeed this is the kind of anamnesis typically explored by the neuropsychiatrist. It is important not to ask direct questions, but allow the patient's personality to reveal itself through openness and their own narrative, then follow up clues that lead to potential diagnoses. Further, symptom development needs to be put into an autobiographical narrative context, and not documented as some abstract collation of facts, assembled into a diagnosis (syndrome), viewed and skewed through one pair of glasses only.

Somatoform disorders

The incidence of conversion or somatoform disorders in neurological practice is often given at around 10%, but one careful survey by a neurologist showed that over one-quarter of neurological out-patient cases finish their consultations with no diagnosis. Another survey gave a figure of 24% of non-organic cases out of 133 female neurology in-patients. These studies alone reveal the above principles – the overlap between neurological symptoms and non-neurological diagnoses, the gap between signs and symptoms and referral patterns to neurologists that are based on social rather than on strict medical grounds.

The frequency of full-blown somatization disorder is clearly less, perhaps up to 1% in the general population but considerably more frequent in neurological settings. The evaluation of such patients requires taking into account not only the past illness history, but also the current mental state in addition to anomalies on physical examination. The latter are often rather ignored: they are remarkably reliable. For example, the Hoover sign in non-neurological hemiparesis, which consistently reveals the non-anatomical nature of the weakness, non-physiological anaesthetic patches, anomalous visual complaints with tubular or spiral visual fields and bizarre but typical hysterical gait must always be incorporated into the diagnostic formulation. A past surgical history is important. Many patients with somatization disorder have had an appendicectomy carried out (for a grumbling, histologically normal appendix) and also gynaecological procedures. With somatization disorder, as the history progresses, patients tend to move towards a neurological setting as their dependency increases. The typical patient is female, 20–30 years old and will have come from a turbulent family background. There is often a family history of alcoholism or sociopathy and it may be possible to elicit a history of some form of abuse, physical or sexual. School refusal and poor academic achievement may also frame their early years. Childhood illnesses are noted (abdominal pains, growing pains, school refusal and the like), or sometimes the person had been described simply as sickly – always ill – in childhood.

Typically, abdominal pains lead to an initial operation, although tonsils and adenoids may have already been removed. Further abdominal problems follow (adhesions are blamed) with further operations (70% have had an appendicectomy; 50% a gynaecological procedure). Other problems arise, diagnoses such as premenstrual tension, irritable bowel syndrome, fibromyalgia and the like are made, but the symptom history is imprecise, and sometimes dramatically described ('I arrested three times in hospital'). Visits to a variety of specialists are recorded and neurologists become involved at some stage. Seizures are a common referral symptom. As dependency increases in the more severely affected cases, contractures, intractable seizures and inevitable loss of motor power leading to a wheelchair-bound existence results. Patients languish at home, in physiotherapy departments, on the wards, often remaining in bed, with their physical state still being trumped with medical diagnoses such as myalgic encephalomyelitis or dystonia (or a well-meaning, 'perhaps you have a touch of demyelination'). Splints are sported, dark glasses donned, catheters inserted, and further dependency ensues. Within the compendium of medications are usually benzodiazepines, opiates and other analgesics. About 10% of these patients become wheelchair-dependent. It is estimated they spend about one-quarter of their waking hours in bed.

Patients with somatization disorder often have an associated personality disorder. This manifests itself as the lifelong tendency to overuse medical facilities, with an excess dependency on caregivers and the revealed abnormal illness behaviour. In other patients, borderline personality attributes are more evident, with emotional lability, episodes of self-harm, substance abuse and an inability to form substantial interpersonal and vocational relationships. The hysterical personality is characterized by excessive dependence, shallow labile affects, impulsivity, a tendency to verbal exaggeration and excessive gesture, seductive behaviour and self-dramatization. It is important to recognize these underlying personality dispositions because they have a bearing on the development of symptoms over time, e.g. through self-harm, or through persuasion of surgeons to carry out unnecessary operations, thus giving patients definitive scars and wounds. Verbal exaggeration combined with an impulsive imprecise cognitive style makes taking an adequate history in such patients very difficult. Misleading conclusions can follow. The importance of obtaining past medical records, especially full previous GP notes, cannot be overemphasized.

Factitious disorders, Munchausen's syndrome and malingering

In factitious disorder, the symptoms and signs of illness are deliberately produced in order to adopt a sick role. Although this disorder overlaps with Munchausen's syndrome and malingering, factitious disorder is differentiated by the fact that physical signs are produced with medical knowledge. Paramedical personnel are over-represented as a result. Individuals may produce signs by colouring their urine with blood, heating thermometers artificially or continually re-infecting skin lesions.

Factitious disorders are more common in females, whereas Munchausen's syndrome is more prevalent in males. The key feature of Munchausen's syndrome is deliberate attendance at hospitals, without medical referral, with pseudomedical and often dramatic complaints. Suggestions that the patient may be referred to a psychiatrist usually leads to immediate self-discharge. Malingering refers to the production of physical symptoms for some kind of personal gain, usually financial, and is not as infrequent as many would have us believe. The neurologist should be particularly alert to such a possibility in patients attending with reference to medico-legal and compensation claims.

Hypochondriasis

Hypochondriasis differs from the conditions described above in being a disorder in which patients are preoccupied with symptoms, fearing they have some dreadful ailment. They have such concern about their physical state that they are preoccupied a great deal of the waking day and fail to be reassured about their health, even if verified by physician after physician. Hypochondriasis is reported in up to 10% of medical in-patient consultations. Unlike somatoform disorder, it occurs with equal frequency in males and females. Unlike the rather vague documentation of the symptoms of those with somatoform conversion disorders, these patients usually keep careful documentation of their illness history and the more obsessional develop all kinds of illness rituals. Delusional varieties are sometimes seen. Patients are demanding, clinging, importuning and ungrateful. Inevitably both patient and physician become dissatisfied with their diagnostic encounters. Eventually, if severe the patient becomes isolated from their weary helpers, their frequent appointments with doctors becoming their main social outlets.

The question of the relative state of consciousness and awareness of patients with this spectrum of diagnoses is often raised. Traditionally, the symptoms of conversion disorder are said to be unconscious, while those of malingering are consciously elaborated. In reality, motivation in this spectrum of disorders varies over time, and it is usually quite impossible for the physician to make anything other than a poorly informed guess about this. Patients themselves at one time may be quite willing to admit to a deliberate exaggeration of symptoms which earlier on had been impervious to everyone, even themselves. In a medico-legal setting, the only way to uncover malingering is either by a self confession, or by video exploration or some other kind of personal inquisition that reveals the claimant to be quite unreliable with regards to the truth.

A rough overall guide to the features of these disorders is given in Table 21.1.

Non-epileptic seizures

These require a special place in neuropsychiatric theory and practice. Over the years, a number of conditions previously referred under the rubric of conversion disorders, such as non-organic spasmodic torticollis, or other variants of dystonia, appear to have decreased in the frequency of their presentations to psychiatry. Conversely, the frequency with which non-epileptic seizures are diagnosed has increased, particularly in specialist centres where the management of difficult epilepsy is undertaken. One reason for this is better evaluation of patients with video-telemetry which reveals a subpopulation of those with previously diagnosed epileptic seizures that are clearly non-epileptic. Another reason is the awareness by neurologists of the frequency of non-epileptic attack disorder.

It is generally accepted that in those diagnosed with intractable epilepsy some 20–25% have entirely non-epileptic seizures. Further, within this same population, about 30% of patients will have co-morbid non-epileptic and epileptic seizures.

When seeing patients presenting with seizures that are difficult to characterize or explain, it is important first to rule out obvious other physical conditions that may be relevant. In particular, the confusion of attacks of syncope for epileptic seizures deserves mention. Thus, many patients with syncope begin their careers with a label of epilepsy having first experienced episodes of loss

Table 21.1 The spectrum of somatoform disorders and variants.

	Hypochondriasis	Somatization disorder	Factitious disorder	Munchausen's syndrome	Malingering
Gender (M)	F = M	F > M	F > M	M > F	M > F
Mono- (M) or poly- (P) symptomatic	P 95%: M 5%	Typically P	M or P	Mostly M	M or P
Personality type	Nil specific	Borderline, histrionic, antisocial	Nil specific	Especially antisocial	Especially antisocial
Associated psychiatric disorder	Depression/anxiety	Depression/anxiety	No	No	Pseudodepression and psychosis
External incentive	No	No	No	Yes	Yes
Special features	High anxiety			Peregrination, dramatic complaints	Compensation setting

Table 21.2 Typical features of syncope, epilepsy and non-epileptic attacks.

	Syncope	Epilepsy	Non-epileptic attack
Eyes	Open, deviated	Open, deviated	Closed
Respiration	Shallow	Sometimes stertorious	Typically increased
Automatism	Brief	Minutes or longer	Usually none
Duration	Brief, <2 min	Often >2 min	Variable, often >2 min
Movements	Myoclonic	Tonic–clonic + frothing at mouth	Stiffness, shaking
Orientation on recovery	Immediate	Delayed	Astonished
Skin colour	Pale	Cyanosis	Normal

of consciousness in adolescence. These episodes are often associated with a brief period of myoclonic jerking which to the untutored eye may be misinterpreted as generalized tonic–clonic jerking. It is often taught that third party reports of attacks are of utmost importance in the diagnosis of epilepsy. Such reports are by no means always helpful. Although of course valuable in some settings, especially if the attack is seen by a health professional familiar with epilepsy, it is often the case that a physician taking the history will put direct questions to the observer, creating an image for both of them that, for example, the brief period of syncopal jerking was an episode of bilateral synchronous muscular movements seen in epilepsy. Clues to the differential distinction between vasovagal episodes, epilepsy and non-epileptic seizures are shown in Table 21.2.

The psychiatric condition most often misdiagnosed as epilepsy is panic disorder. The paroxysmal nature of the attacks, with rapid onset and with an associated self-report of loss of consciousness, hints at a complex partial seizure. Patients with panic disorder tend to have attacks that are less stereotyped and of longer duration than epileptic seizures. In addition, unlike most epilepsy patients, they have post-attack anxiety symptoms often lasting hours and a history of an anxiety-related disorder. Panic attacks may be triggered by stressful events, but so may epileptic seizures.

One variant of panic disorder is referred to as panic disorder *sine* panic, the patient denying or not experiencing the typical symptoms of panic. This represents one form of dissociation. With careful questioning it becomes clear that the patient does not actually lose consciousness completely, but has an altered awareness and a dim reflection of events going on around them.

Table 21.3 (a) Clues to a diagnosis of non-epileptic attacks.

- Frequent seizures with a normal EEG (ictal or interictal)
- Status epilepticus, especially repeated status (is rare) with normal ictal or interictal EEG
- Past psychiatric history, especially personality disorders
- Paramedical professions
- Variability of phenomenology, multiple seizure descriptions
- Pelvic thrusting seen during the attack (seen with frontal seizures but rarely)
- Crying and emotional displays after the attack
- Failure to respond to antiepileptic drugs with some features above

A number of clinical clues to the diagnosis of non-epileptic seizures are given in Table 21.3(a). A practical guide is that the patient who experiences many seizures a day and who has a normal interictal EEG either has seizures with a deep-seated frontal focus or has non-epileptic seizures. However, in such frontal seizures, in which bizarre uncoordinated movements can occur, the attacks can appear to the untutored eye to be non-epileptic; the ictal EEG with surface electrodes is also sometimes deceptively normal.

About 70% of patients with epilepsy respond well to standard antiepileptic therapy. Failure to respond, with continuing frequent attacks and a normal interictal EEG, should raise doubts about the diagnosis.

Status epilepticus is quite rare. It is estimated that some 50% of patients admitted to ITU with status epilepticus actually have non-epileptic status. Thus, repeated bouts of apparent status epilepticus with a normal interictal EEG again suggest non-epileptic

Table 21.3 (b) Common myths about features said to suggest epilepsy that may well occur in non-epileptic attack disorder (NEAD).

Myth	Comment
Self-injury is common in epilepsy but not in NEAD	Self-injury is common, especially carpet burns in NEAD
Urinary incontinence is uncommon in NEAD	Urinary incontinence is of little diagnostic value; it occurs infrequently in NEAD
An abnormal interictal EEG does not always mean an epileptic seizure	Many patients with epilepsy also have NEAD
Third-party eye-witness descriptions are very valuable and reliable	Third party eye-witness descriptions can also be misleading

attacks. Any hint that it took 'seven men to hold the patient down' is not likely to be referring to an epileptic seizure.

The patient who reports several different kinds of event probably has either non-epileptic attacks or a combination of the latter with epilepsy. Further, variability in the semiology of the attacks over time is more in keeping with non-epileptic attacks than with epilepsy.

Incontinence is of little diagnostic help. However, injuries are frequently seen in patients with non-epileptic attacks. They tend to have a different quality and occur at different sites from those injuries seen in epilepsy. Generally, in epilepsy, the bony prominences are damaged as the patient falls and hits their limb or head on protruding objects. Lesions are thus often found under the chin or under the eyebrows, the nose may be broken, and bones fractured. In non-epileptic attacks, the injuries are often carpet burns on the forehead, cheek, elbows or knees. Fractures are rare and burns from scalding very rare. Repetitive injury to the same part of the body or opening up wounds are highly suggestive of non-epileptic attacks. Table 21.3 (b) summarizes some diagnostic hints and myths surrounding non-epileptic attacks.

Psychogenic movement disorders

Like non-epileptic attacks, this well-recognized entity deserves special mention. Its history is revealing. It was clearly recognized in the 19th century, by neurologists such as Charcot, that patients developed all kinds of movement disorders, some acute and others chronic. Most of these conditions were, for Charcot, variants of hysteria. With the discovery of levodopa in the 1960s and the realization of close links between movement and dopamine, the idea that some movement disorders could have non-neurological antecedents tended to rejected. Almost all abnormal movements were considered organic and thus neurological. However, in the last two decades the concept of psychogenic movement disorders has undergone a certain revival

A variety of presentations are now recognized, from psychogenic parkinsonism through to tremors, gait disorders, and tics and myoclonic jerks. Estimates suggest that 3–25% of patients attending movement disorder clinics probably have some form of psychogenic movement disorder. Ten per cent of patients diagnosed as having Parkinson's disease have a normal DAT scan.

Psychogenic dystonia is one interesting variant. Patients frequently present with a focal dystonia, e.g. as a spasmodic torticollis, but it is often more widespread and can involve the trunk, leading to bizarre posturing. The abnormal movements may come on quite suddenly and can be precipitated by minor trauma. In the upper limb, dystonia begins with contraction and flexion of the fingers, then affects the wrist and eventually moves up the arm. In the legs, classically the foot becomes inverted. Eventually the patient begins to walk entirely on the lateral border of the foot and even on the dorsum. There are overlaps between psychogenic dystonia and the causalgia-dystonia syndrome and regional pain syndrome also called reflex sympathetic dystrophy.

Table 21.4 Diagnostic features pointing towards psychogenic dystonia. After Fahn & Williams (1988).

- False weakness
- Sensory complaints, severe pain and false sensory findings
- Multiple somatizations
- Self-inflected injuries
- Obvious psychiatric disturbances
- Inconsistent dystonic movements over time
- Incongruous dystonic movements and postures
- Dystonia usually presents as a fixed dystonia or as a paroxysmal dystonia
- Other movement disorders, usually presenting as incongruent or bizarre movements including bizarre gait and often as a paroxysmal disorder

In contrast to organic dystonias, the psychogenic dystonias are characteristically fixed, the patient being unable to move the affective part and they are sometimes initially painful. Any initial causalgia tends to wane. The dystonia may become progressive. Having first affected the lower limb on one side it can spread to the other or even to all four limbs. It is not unknown for amputation to be carried out by surgeons unfamiliar with the condition. Table 21.4 lists some clues to the diagnosis of psychogenic dystonia. There is an overlap with multiple somatizations and also a link with factitious disorder and malingering. Psychogenic dystonia is not improved with sleep. The patient commonly shows a slowness of any voluntary movement and a curious resistance to passive movement: resistance from the patient increases as the examiner, when testing a movement, gradually increases force. With organic spasmodic torticollis many patients develop curious tricks to reduce abnormal head posture, e.g. moving a hand to touch the chin or neck. These movements are known as g*estes antagonistes*, and are not reported in psychogenic dystonia.

Some basic psychiatric principles

Personality disorders

It is important for an assessment of a patient's personality to be taken into account when trying to understand neurological symptoms generally but particularly so where there is some failure of symptoms and/or signs to correspond to the neurologist's expectations. A brief overview of the more important terms for neurological practice is given here.

It is useful to begin with distinctions made between psychogenic development and organic process. The psychopathologist Karl Jaspers put it thus: 'We differentiate abnormal personality types that are anlage (genetic predisposition to a given trait or personality characteristic) variants, the sick personalities in the narrower sense, from those where a change has been brought about by a process.' Thus, personality change induced by a process, either a neurological illness or a psychiatric disorder, needs to be distinguished from the enduring characteristics by which we come to know a person over time. In psychiatric settings several different personality styles are recognized that have clinical importance. Those of most relevance to neurologists are briefly noted here. The fuller details of these disorders can be found in standard diagnostic manuals.

The term 'psychopathic personality' implies antisocial personality traits; sociopathy, sociopathic personality and antisocial personality are alternative terms. This personality type is characterized by a disregard for social obligations, a lack of feeling for others, cruelty, impetuous violence or callous unconcern. Such a personality emerges from an early life history of conduct disturbance at school, with disturbed family relationships leading to a poor work record and difficulty forming enduring interpersonal relationships. An interesting feature of the psychopathic personality is the tendency to remit or improve over time. The onset of such a personality style in midlife usually implies the development of an underlying process – organic, psychological, or both.

The obsessional personality is characterized by a lifelong tendency to meticulousness and punctuality. Patients have difficulty in expressing their emotions. They check and recheck their actions. Many patients attending clinics with neurological symptoms but no obvious neurological disease have such a personality style. The meticulous circumstantiality of these patients can make history-taking a laborious process and obtaining what is relevant may be difficult. This cognitive style is to be contrasted with the features of the hysterical personality, whose impressionistic views of their own world have already been mentioned.

The paranoid personality is distinguished by continued suspiciousness and excessive sensitivity. Schizoid personalities have little affective or social contact with others and have a tendency to detachment and eccentricity. The borderline personality is particularly important to recognize in neurological practice because the tendency to somatize often presents with somatic symptoms that have no neurological substance. The personality style is characterized by unstable personal relationships, impulsivity that often leads to self-harm or outbursts of intense anger, affective instability and sometimes transient paranoid episodes. They seem particularly susceptible to dissociative episodes which may underpin a presentation with non-epileptic attacks.

Anxious personality defines those who display lifelong anxiety and who, under stress, readily develop anxiety or panic disorders. In a neurological setting they appear with fleeting neurological symptoms. Panic disorder is probably the psychiatric disorder most commonly misdiagnosed as epilepsy.

Finally of some neurological relevance is the explosive personality. This defines those who are liable to intemperate bursts of anger but who do not otherwise have the characteristics of the psychopathic personality. Such patients have paroxysmal episodes of rage, referred to as episodic dyscontrol.

In contrast to the above, the anlages of Jaspers, neurological processes that lead to personality changes, are referred to by the all-embracing term 'organic personality change'. Damage or disease processes of the frontal and temporal lobes are most likely to be involved, providing an identifiable stamp on the person's behaviour which is recognized clinically as bringing about a change in their behavioural patterns.

Following this account of some of the more relevant personality disorders, some important psychiatric diagnoses met in neurological settings are discussed. It should at this point be made clear that the following psychiatric disorders can develop in patients with any style of personality. However, some personality disorders lend themselves to certain psychiatric diagnoses, e.g. the continually anxious is more liable to develop anxiety disorder, and the anankastic or obsessive will have an increased tendency to develop an obsessive-compulsive disorder. As noted, neurological disease is a powerful influence on personality and changes of personality combined with the development of psychiatric illness can represent a difficult diagnostic conundrum.

Anxiety disorders

The hallmark of an anxiety disorder is the anxiety itself. The most important disorders are panic disorder with or without agoraphobia, generalized anxiety disorder, specific phobias, post-traumatic stress disorder and obsessive-compulsive disorder.

The manifestations of the anxiety are multiple and affect every bodily system. Because the symptoms of anxiety are so common and lead to the reporting of somatic symptoms, patients with anxiety disorders are often referred for unnecessary investigations and treated inappropriately.

Common symptoms include palpitations, sometimes associated with anterior chest pain, dyspnoea with a sense of choking and not being able to get enough breath, dry mouth often with an unpleasant metallic taste, abdominal tension associated with nausea and sometimes even vomiting, constipation and diarrhoea, urinary retention, poor concentration and memory, dizziness, vertigo, fainting feelings and on occasion blackouts which can resemble epileptic seizures. Other symptoms include fatigue and loss of energy, sensory symptoms such as tingling, and diminished vision or auditory hyperaesthesia in which sounds are distorted or magnified.

In panic disorder, relatively frequent discrete episodes of panic are associated with apprehension and fear. The paroxysmal nature and sudden onset of these episodes in which an obvious precipitating factor may be unclear can lead to a diagnosis of a complex partial seizure. A variant of this disorder is the phobic anxiety depersonalization syndrome. This can be a much more pervasive disorder with generalized anxiety, affective symptoms and a substantial risk of suicide. In some patients depersonalization may persist and become chronic. Other patients complain that they feel like automatons. Such symptoms, when prolonged, are very unpleasant.

In neurological practice, anxiety states are misinterpreted as epilepsy, vertigo, benign essential tremor, multiple sclerosis and even states of dementia. Hyperventilation is common, although patients are often unaware that they are hyperventilating. This leads to neurological symptoms with a worsening of the anxiety and can ultimately present as episodes of loss of consciousness.

Post-traumatic stress disorder has become a popular diagnosis. The clinical criteria have changed over time to become less rigid but the essence of the syndrome, referred to at one time as post-traumatic neurosis, is the development of a combination of anxiety and other affective symptoms following a specific stress. A special emphasis is given to the re-experiencing of a trauma psychologically, usually in the form of flashbacks or nightmares. The former may be triggered by specific stimuli reminiscent of the original trauma. The other symptoms are related to the development of avoidance of stimuli that remind the patient of the psychological trauma, and a numbing of emotional responses. Patients typically will not talk about what has happened, they avoid watching television programmes that may be in some way associated with their trauma and develop cognitive strategies to divert their thinking away from unpleasant thoughts. Two symptoms are of particular interest in neurological practice. One is the increased startle response which can be so severe to be misdiagnosed as startle epilepsy or Gilles de la Tourette's syndrome. The second is psychogenic amnesia. Patients are simply unable to remember the details of their traumatic event, which in patients who have had some kind of head injury may be misinterpreted as an organic post-traumatic amnesia. The current diagnostic criteria for post-traumatic stress disorder are shown in Table 21.5.

Table 21.5 Post-traumatic stress disorder (DSM-IV-TR criteria).

A The person has been exposed to a traumatic event in which both of the following were present:
1 The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others
2 The person's response involved intense fear, helplessness, or horror. Note**:** In children, this may be expressed instead by disorganized or agitated behaviour

B The traumatic event is persistently re-experienced in one (or more) of the following ways:
1 Recurrent and intrusive distressing recollections of the event, including images, thoughts or perceptions. Note**:** In young children, repetitive play may occur in which themes or aspects of the trauma are expressed
2 Recurrent distressing dreams of the event. Note**:** In children, there may be frightening dreams without recognizable content
3 Acting or feeling as if the traumatic event were recurring (including a sense of reliving the experience, illusions, hallucinations and dissociative flashback episodes, including those that occur on awakening or when intoxicated). Note**:** In young children, trauma-specific re-enactment may occur
4 Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
5 Physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event

C Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:
1 efforts to avoid thoughts, feelings, or conversations associated with the trauma
2 efforts to avoid activities, places, or people that arouse recollections of the trauma
3 inability to recall an important aspect of the trauma
4 markedly diminished interest or participation in significant activities
5 feeling of detachment or estrangement from others
6 restricted range of affect (e.g. unable to have loving feelings)
7 sense of a foreshortened future (e.g. does not expect to have a career, marriage, children, or a normal life span)

D Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:
1 difficulty falling or staying asleep
2 irritability or outbursts of anger
3 difficulty concentrating
4 hypervigilance
5 exaggerated startle response

E Duration of the disturbance (symptoms in Criteria B, C, and D) is more than 1 month

F The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

Specify if:
Acute: if duration of symptoms is less than 3 months
Chronic: if duration of symptoms is 3 months or more

Specify if:
With delayed onset: if onset of symptoms is at least 6 months after the stressor

Obsessive-compulsive disorder is not uncommon in neurological practice. The anankastic personality may be over-represented in those presenting with unexplained neurological symptoms. A secondary obsessive-compulsive disorder is reported in post-encephalitic parkinsonism, in some cases the compulsions being awakened by levodopa. In Gilles de la Tourette's syndrome approximately 50% of patients display obsessive-compulsive behaviour and a co-morbid obsessive-compulsive disorder is commonly found. In this condition, in which multiple tics – including vocal tics – present as a chronic disorder, other interesting features include complicated stereotypes and rituals, echo and copro phenomena and, in about 30% of patients, compulsive self-harm. Obsessional slowness can sometimes be so excessive that patients will hardly move, e.g. for fear of catching something by touch. This can even be misinterpreted as a movement disorder linked to a failure of motor planning.

Affective disorders

The term 'affective' generally means that condition in which an alteration of mood is the central feature. As such, disorders of affect – particularly depression – are frequently encountered in neurological practice. However, in the clinical setting a common but important error is to confuse depressive symptoms, sadness and demoralization in the setting of physical illness with a depressive illness itself. The latter has quite specific features, central being the disturbance of mood, which is prolonged and continuous. Episodes of more transient changes of mood are often referred to as dysthymic disorder. In the assessment of depressive symptoms, personality factors are often insufficiently taken into account, particularly premorbid neuroticism, and in reality many patients with dysphoric symptoms have long-standing personality disorder and tolerate life's stresses poorly.

The change of mood in depressive illness is associated with a loss of vitality; the patient ceases to enjoy life and has loss of emotional well-being. Libido is diminished. Concentration difficulties, with complaints of poor memory, increased apathy with diminution of movement, loss of appetite and alteration of the sleep pattern are noted. Patients will complain that food is tasteless; they may lose weight; they have nocturnal restlessness and may have typical early morning waking with morbid ruminations and a feeling of being unrefreshed by sleep. Diurnal variation is sometimes reported, with symptoms improving as the day progresses.

Feelings of anxiety and tension are invariably present. Some patients, in contrast to having psychomotor retardation, become agitated with indecision and display excessive motor activity. In the extreme form intense aimless pacing is seen.

Some patients with depression do not report or under-report any change of mood, and present with somatic symptoms referable to any part of the body. The latter then become the focus of attention for both patient and physician, leading to unnecessary investigations and a failure to diagnose the underlying disorder of mood.

It is important to enquire about suicidal ideas that may be embedded within other thoughts of worthlessness, guilt and a certainty that the patient has let people down. Increased irritability, hostility and even overt aggressive episodes may develop, especially in the family setting, leading to considerable distress. This can obstruct the diagnosis of the depression.

The above mental states need to be distinguished from the lability of mood seen in pseudobulbar palsy or in a frontal lobe syndrome in which rapid oscillations between one mood state and another are seen such as excessive laughing and crying.

Mania is an alternative affective state, hypomania being a less severe clinical presentation of an upswing in mood. Usually patients have bipolar expressions referred to in the past as a manic depressive disorder. There is an increased sense of well-being. The patient expresses euphoria, they may demonstrate accelerated thoughts with a flight of ideas and pressure of speech. Motor activity is excessive. Concentration is poor, patients are distractible and irritable, sleep is brief and appetite increased. In classic mania, patients are restless, they show disordered speech with rhyming, punning and wordplay and their mood is more dysphoric than euphoric.

Depression in neurological disorders

In some patients depression is not occasioned by some life crisis, a genetic miss-gift or an understandable consequence of a chronic physical disorder. Depression can be directly interlinked with a neurological condition touching therefore on the neuroanatomical and neurochemical underpinnings of affective expression. The reported frequency of depressive illness in neurological disorders is shown in Table 21.6.

However, even in these settings the symptoms of the depression may be subtly different from those of a typical depressive illness in the absence of neurological illness. For example, in Parkinson's disease an excess of anxiety is reported, while in epilepsy some episodes are brief with excess of irritability and dysphoria, the so-called interictal dysphoric disorder. The depression secondary to cerebrovascular disease may present with quite bizarre somatic symptoms with delusional features, and depression secondary to Huntington's disease is linked with a high frequency of suicide. Some of these associations are discussed further below.

Several neurological disorders have been associated with secondary mania (Table 21.7).

Interestingly, most reported cases of mania in this setting emphasize damage to the right hemisphere and involve either the orbital frontal cortex, caudate nuclei, thalamus and/or medial-temporal areas. There is thus an association with the cortical–subcortical circuits briefly described below. As with depression, the clinical picture of these neuropsychiatric disorders is often different from an equivalent psychiatric disorder where no underlying neurological damage is apparent. The manias can erupt suddenly without any prior history or genetic backing. The associated delusions are often unusual. In Parkinson's disease delusions are often occupational or linked with some past situation (e.g. service in the armed forces) and the accompanying hallucinations are complex and visual. In epilepsy they are often religiose. In syphilitic general paralysis delusions tend to be grandiose and extravagant.

Table 21.6 Depression in neurological disorders. From Cummings & Trimble (2002).

Neurological condition	Frequency of depressive syndromes (%)	Characteristics of depressive syndrome
Stroke	30–60	Psychomotor retardation often severe; depression more common in patients with brain atrophy, with left frontal and left caudate lesions and when lesion approaches left frontal pole
Parkinson's disease	30–50	Anxiety common; mood-congruent delusions; suicide rare. PET: diminished orbito-frontal + caudate glucose metabolism
Huntington's disease	35–45	Suicide common. PET: diminished orbito-frontal glucose metabolism
Epilepsy	10–50	Frequency of suicide and delusions increased. PET: diminished orbito-frontal or left brain glucose metabolism
Traumatic brain injury	25–50	History of psychiatric disorder (including substance abuse) common among those who develop post-traumatic depression
MS	25–50	Depression often not related to degree of disability
Alzheimer's disease	30–40	Major depressive episodes rare; depressive symptoms common
Vascular dementia	25–60	Depression common in lacunar state and Binswanger's disease

MS, multiple sclerosis; PET, positron emission tomography.

Table 21.7 Neurological disorders associated with secondary mania. From Trimble (1996).

Stroke
Temporal lobe tumours
Epilepsy
Parkinson's disease with dopamine agonist therapy
Idiopathic basal ganglia calcification (Fahr's disease)
Huntington's disease
Traumatic brain injury
Multiple sclerosis
Frontal lobe degeneration
Cerebral syphilis

Note: most reported cases where laterality can be established affect the right hemisphere.

Psychoses

The term 'psychosis' generally refers to a condition in which there are hallucinations and delusions associated with abnormalities in behaviour in which insight is diminished or lost. Excitement and over-activity or psychomotor retardation and even catatonia occur. In contrast to disorders of affect, psychotic states, although implying a severe disturbance of psychological function, are less often encountered in neurological practice. Ontologically the brain must allow the individual to interpret the world in a logical and adaptive way. Hallucinations and delusions suggest deviant processing and underlying this are disturbances of neurological function secondary to structural disease. Hallucinations are perceptions in the absence of an adequate sensory stimulus. They must be distinguished from illusions which are misinterpretations of perceptions. Pseudohallucinations are hallucinatory experiences that occur in subjective rather than objective space, are less clearly delineated and often perceived as being unreal. Thus, they lack the objectivity of hallucinations proper. The latter have concrete reality, are substantial and linked with a lack of insight into their nature.

Table 21.8 Brain disorders associated with delusions. From Cummings & Trimble (2002).

Schizophrenia
Mania with psychosis
Depression with psychosis
Epilepsy (especially temporal lobe epilepsy)
Alzheimer's disease
Fronto-temporal dementias (e.g. Pick's disease)
Dementia with Lewy bodies
Huntington's disease
Parkinson's disease after treatment with dopaminergic agents
Idiopathic basal ganglia calcification
Post-traumatic encephalopathy
Viral encephalitis (especially herpes simplex encephalitis)
Creutzfeldt–Jakob disease
Stroke (particularly involving the temporal lobes, such as in Wernicke's aphasia)
Wernicke–Korsakoff syndrome
Vascular dementia
Multiple sclerosis
Porphyria
Metachromatic leucodystrophy
Adrenoleucodystrophy
Brain tumours (particularly involving temporal lobes, R > L)
Vitamin B_{12} deficiency
G_{M2} gangliosidosis
Neuronal ceroid lipofuscinosis
Mitochondrial encephalopathy
Prader–Willi syndrome (excessive appetite, etc.)

Delusions are unshakable convictions that are manifestly incorrect. They have to be interpreted within the cultural setting of the patient, but it is the tenacity with which patients hold on to their beliefs against all logic that inevitably reveals the delusion. They need to be distinguished from over-valued ideas which are strongly held beliefs that are not incorrigible. Neurological conditions associated with delusions are shown in Table 21.8.

Delusions are the hallmark of a paranoid illness and occur in a spectrum of psychiatric disorders including schizophrenia. In the affective disorders they are characteristically mood congruent, whereas mood incongruent delusions are typical of schizophrenia. In the Capgras syndrome a significant person in that patient's life is replaced by a supposed identical double, while in the Fregoli syndrome a supposed persecutor can change his or her appearance and appear as other people. These are referred to as misidentification syndromes.

In depressive disorders hallucinations are characteristically morbid and often refer to the body, for example, being afflicted by some terrible disease. Auditory hallucinations are damning and condemnatory. Visual hallucinations are exceptional. The latter are more characteristic of organic brain syndromes in which settings they may be florid, frightening and often dimly perceived as unreal. Hypnogogic and hypnopompic hallucinations occur as patients are falling asleep or awakening, respectively. They may be auditory, visual or tactile and can be terrifying.

Hallucinations that occur in clear consciousness for which there is no insight and which are mood incongruent are very suggestive of schizophrenia. In this condition the hallucinations are usually auditory although patients may experience them in any modality. Specific auditory hallucinations are noted in association with schizophrenia and constitute some of the Schneiderian First Rank symptoms. These are listed in Table 21.9.

When present in clear consciousness such hallucinations and delusions usually signify schizophrenia, although this is not diagnostic because they are sometimes noted in other psychotic disorders, e.g. in mania. The diagnosis of schizophrenia can also be made in their absence, based upon history and other observed abnormal behaviour.

Visual hallucinations, particularly of small animals, are characteristic of delirium tremens. Formication, the sensation of ants crawling under the skin has been associated with cocaine psychosis. Olfactory hallucinations are reported in schizophrenia and in simple partial seizures of uncinate origin. In epilepsy these experiences are typically brief, unpleasant, hard to characterize and consistent in their phenomenology. In schizophrenia they are much more variable and can last for hours at a time. In coenaesthetic hallucinations the body or part of the body will feel distorted often in quite fantastic ways. While often reported in schizophrenia such hallucinations can occur in migraine or following stroke.

Table 21.9 Psychosis: First Rank Symptoms of Schneider.

Alone, these are not diagnostic of anything, but when present in the setting of clear consciousness support a diagnosis of schizophrenia:

- Thought insertion
- Thought withdrawal
- Thought broadcasting
- Hearing one's thoughts spoken aloud
- Hearing voices arguing about or discussing one
- Hearing voices comment on one's actions
- Delusional perception: abnormal significance attached to a real perception with no logical explanation
- Experiencing bodily sensations as if imposed from outside
- Experiencing affects as if imposed and controlled from outside, e.g. mood change
- Experiencing impulses as if imposed and controlled from outside
- Experiencing motor actions as if imposed and controlled from outside

A characteristic feature of schizophrenia is alteration of thought and language and this may vary from a subtle flattening of the expression and concrete thinking to florid schizaphasia. In this, neologisms (paraphasias), loose connections between thoughts, tangential thinking and intrusive delusional content can lead to a veritable word salad. Sometimes features suggestive of Wernicke's aphasia may be present.

Other clinical neuropsychiatric syndromes

Fugue states refer to episodes of wandering in which patients either complain of, appear to have, or confess to, amnesia for a period during which, for example, they will have left home and appear at a destination in an apparently confused state. During the fugue, in contrast to an epileptic automatism, patients maintain good contact with their surroundings and rarely draw attention to themselves. There may be a complete loss of personal identity and autobiographical memory extending back many years. The most common association of fugues is with an underlying depressive illness but there may be an association with compulsive lying and possibly a minor concussive head injury. Fugues last much longer than epileptic automatisms. In the latter the accompanying confusional state is usually obvious. In transient global amnesia (TGA; Chapter 7) there is sudden onset of amnesia but personal identity is retained and significant persons usually readily identified. When the TGA episode is complete there is amnesia for the period of the event with prompt return of clear awareness. Somnambulism refers to episodes of nocturnal wandering in which patients behave in a semi-purposeful way and again express amnesia for what has happened.

Catatonia is characterized by mutism and bizarre motor activity that ranges from stupor to episodes of agitated excitement. Sustained postures and waxy flexibility of the limbs may be present, associated features being negativism, echo phenomena, stereotypies and mannerisms. There is a wide differential diagnosis embracing many neurological and psychiatric disorders from encephalitis and metabolic disorders to depression and schizophrenia. Lethal catatonia is a rare psychosis in which catatonia is associated with intense autonomic activity and fever: the condition has links with the neuroleptic malignant syndrome (Chapter 18) but it was observed in the pre-neuroleptic era.

Psychiatric disorders secondary to neurological illness

Underlying neuro-anatomical concepts

Although this is not the appropriate place to discuss neuroanatomy in any depth, some of the underlying principles of neuropsychiatry are embedded in neuroanatomy in a way that the 'new neuroanatomy' of the past 30 years has unravelled.

In 1994, the Nobel scientist and neurobiologist, Sir Francis Crick, wrote of his 'astonishing hypothesis': 'You, your joys and your sorrows, your memories and ambitions, your sense of personal identity and free will are in fact no more than the behaviour of a vast assembly of nerve cells and their associated molecules.' The astonishing feature of this hypothesis is why it should be, at the turn of the second millennium, astonishing at all. After all, Hippocrates had presented the same hypothesis some 2500 years earlier. Writing about epilepsy, then referred to as 'the sacred disease', he opined that: 'Men ought to know that from the brain and from the brain only, arise our pleasures, joys, laughter and jests as well as our sorrows, pains, griefs and tears.' In his own philosophy, the brain was considered the seat both of madness and of epilepsy. Neuroscience has taken a veritable backseat in the public and scientific imagination for such a long time that even in the current era the concept that the brain is the central organ of thoughts, feelings and emotive energy and that without the human brain there is no human endeavour, is still found astonishing. It is a fact, not an hypothesis, that consciousness, awareness and all that flows from them are dependent on the brain and its functioning in an appropriate manner.

Although great strides in neuro-anatomy and neurophysiology were made in the 19th century, little progress was made in understanding how emotions were represented neurologically. The James–Lange hypothesis suggested that the emotions were derived from sensory inputs to the brain which activate motor outputs and thus the resulting bodily sensations are perceived as the emotion. For example, this hypothesis suggested that we do not run away from something because of fear but we experience fear because we are running away. However, with such theories there were no obvious cerebral locations for the generation of the emotion, although the sensory experiences were known to be received cortically, namely in the parietal regions of the brain.

The James–Lange hypothesis was soon tested and shown to be wrong, from two avenues. First it was shown in animals that removal of the cortex of the brain on both sides did not abolish the expression of emotion. Further, it was revealed that stimulation of various structures buried deep within the brain could lead to the release of emotion. These observations formed the basis for a neuroscientific revolution, the impact of which is still poorly appreciated, not only by many in the scientific community – hence Crick's astonishment – but also by the public and media generally.

The limbic lobe

The unravelling of the cerebral mysteries of our emotional being has been one of the most fascinating neuroscience endeavours of the last hundred years. We now appreciate that certain brain structures and pathways are crucial for the mediation and experience of emotion and these are parts of our old evolutionary inheritance that developed aeons before *homo* developed into *sapiens*.

The key structures of the limbic lobe are the amygdala and the hippocampus, both neuronal aggregates of considerable complexity, and their immediate connecting structures, such as the orbital part of the frontal cortex and the ventral striatum, that part of the brain's extrapyramidal system that relates to emotional motor expression. Each amygdala is located at the anterior part of the temporal lobe and is central to the brain's regulation of emotion.The lateral cortical part has extensive connections with the neocortex, from which it receives polysensory information; a central–medial division forms part of the extended amygdala. The amygdala provides affective valence to sensory representations and is crucial for the emotional tone of memories. The amygdala thus has reciprocal connections with the same cortical structures it receives information from, including even the primary sensory cortical areas allowing for an influence of emotional tone directly on cortical sensory impressions.

The hippocampus is also situated in the temporal lobe, an elongated structure composed of several subdivisions, together referred to, with the dentate gyrus, as the hippocampal formation. The main outflow path of the hippocampus is the fornix, which like several other limbic components curves around the thalamus and then descends to the mammillary bodies of the hypothalamus, forming a crucial link structure still referred to as the Papez circuit. The latter name refers to an initially identified collation of structures that modulated emotion and for the first time gave the emotional disorders (psychiatry) a firm neuro-anatomical base. Other crucial structures include the parahippocampal gyrus and the entorhinal cortex which input much integrated polysensory information to the hippocampus via the perforant path. The cingulate gyrus surrounds the corpus callosum forming a C-shaped band, linking posteriorly with the parahippocampal gyrus connecting extensively with neocortical structures, such as the precuneus. The gyrus has widespread connections with the entorhinal area, the amygdala, the ventral striatum, the hypothalamus and subcortical structures which allow the cingulate gyrus to have a very important role in attention, motivation and emotion. The inputs to the limbic lobe are thus both interoceptive (visceral) and exteroceptive (conveying information about the environment). The former derive from many structures that give information about the internal state of the organism, and include modulating influences from substantial neurotransmitter autonomic pathways which originate in the mid- and hindbrain that help drive behaviour and modulate mood, via transmitters such as dopamine, serotonin and noradrenaline. The exteroceptive afferents derive from all sensory systems and ultimately present complex integrated sensory information from the cortex to the hippocampus and the amygdala (Chapter 2).

The frontal lobes of the brain have many demarcated subregions. The orbital, medial and dorsolateral areas are those most frequently discussed. The orbito-frontal cortex lies over the floor of the anterior cranial fossa and has intimate connections with the anterior insula, the amygdala, the ventral striatum and sensory projection pathways.

The insula is a large limbic structure, which in contrast to most of the limbic lobe is not visible from the medial surface of the brain. It lies laterally, buried beneath folds of neocortex. This too has many functions, including integration of limbic and cortical information and it links with the frontal cortex anteriorly and with the hippocampal structures posteriorly.

An understanding that the cortical afferents to the corpus striatum involve the whole of the cortical mantle, including from the limbic lobe, has allowed for a theoretical differentiation to be made between the ventral and dorsal striata, respectively receiving their main inputs from the limbic lobe and the neocortex. One main area of the ventral striatum is the accumbens, heavily afferented from the cortical amygdala and hippocampus, and the prefrontal and temporal association cortices. The main output from the ventral striatum is to the ventral globus pallidus and thence to the thalamus which then projects back to the frontal cortex. This is but one of several cortico-striato-pallidal-thalamic-cortical parallel re-entrant loops, possibly segregated that have been defined in the vertebrate brain and have important regulatory properties governing behaviour. The loop from the motor cortex (dorsal striatum) is involved with somato-motor activity, while the ventral limbic–striatal circuits modulate reward and motivation. However, there are efferents from the ventral to the dorsal striatum. The so-called extended amygdala forms a bridge between the amygdala (central and medial nuclei), the limbic forebrain (ventral striatum) and the hypothalamus, with its autonomic and endocrine influences. These anatomical principles reveal how emotion drives motion, providing an understanding of the motor aspects of all psychiatric disorders and the emotional dysfunction that accompanies many neurologically described disorders, especially disorders of movement.

The concept that certain major brain structures could form the foundation of an emotional brain system was a stunning departure for neurology and the launch pad of the discipline of behavioural neurology – that branch of neurology which tries to understand how the brain modulates and relates to behaviour. This also gave a neuro-anatomical framework for the renaissance of neuropsychiatry.

A problem with the initial conceptions of the limbic system (which became viewed as a self-contained system, hence the preferred term 'limbic lobe' – after Broca), were the earlier accepted anatomical facts which suggested that there were very few direct cortical projections from the neocortex to the hypothalamus (a structure that is so important in regulating autonomic activity), and that the hypothalamus was to be regarded as the principal subcortical projection of the limbic system. This led to an interesting but damaging conclusion that had implications not only for understanding brain behaviour relationships but also for the developing fields of behavioural neurology and neuropsychiatry. Thus, those neurologists who 50 years ago might reluctantly concede that there was an underlying neurology of behaviour, would say that the limbic system–hypothalamic axis was explanatory enough for them – it explained how there might be a neurology of the emotions (and hence a biological psychiatry). This was very different from the known neuro-anatomy of neurological disorders. The latter involved essentially the neocortex and its main outputs, especially the basal ganglia and the pyramidal motor system. A fundamental flaw in this scheme was that it did not correspond to many clinical observations in which a blending of neurological and psychiatric signs and symptoms were seen. Also, it also failed to connect with everyday observations and language, namely that (in English, for example) emotion is six-sevenths movement (e + motion). We express our states of distress and emotion with movements, including of course speech. This conceptual change is shown in outline form in Figure 21.1. Once it became appreciated that the rostral parts of the basal ganglia, far from being exclusively motor in function were actually innervated by the limbic structures and that there was a much stronger connectivity between limbic structures and the basal ganglia than with the hypothalamus, our understanding of the neuro-anatomical basis of neuropsychiatric disorders changed fundamentally.

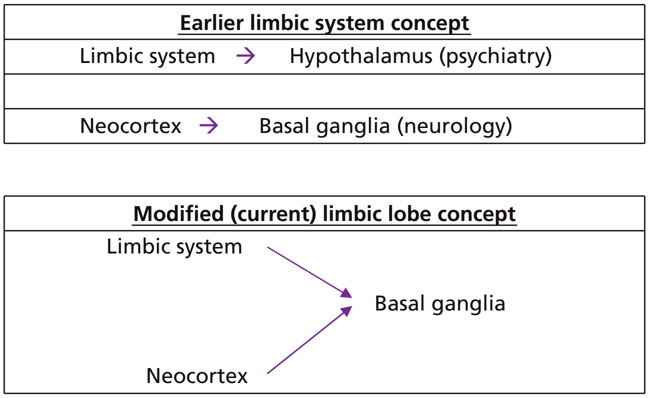
Earlier limbic system concept
Limbic system → Hypothalamus (psychiatry)
Neocortex → Basal ganglia (neurology)
Modified (current) limbic lobe concept
Limbic system
Basal ganglia
Neocortex

Figure 21.1 Concepts of the limbic system.

Epilepsy

Epilepsy is central to the discipline of neuropsychiatry. Seizures are not the same as epilepsy. Each has a separate classification developed by the International League Against Epilepsy. Seizure classification allows for a variety of clinical signs and symptoms, while that of the epilepsies relates more to underlying biological processes. Antiepileptic drugs are in fact not antiepileptic; they are antiseizure medications. To date there is scant evidence that they halt or ameliorate the process of the underlying epilepsy. This means effectively that suppression of seizures, the goal of treating epilepsy, may not lead to an end of a patient's difficulties and is a signal that suppression of seizures in the setting of continuing underlying neurophysiological abnormalities may sometimes have adverse consequences. A classic example is the phenomenon of forced normalization described below.

Psychiatric disorders of epilepsy

A classification of the behaviour disorders encountered in patients with epilepsy must embrace the straightforward psychiatric symptoms that any patient with epilepsy may have, e.g. depression or anxiety that would follow DSM-IV-TR or other psychiatric classifications. However, there are seizure-related and epilepsy-related psychiatric disorders as shown in Table 21.10.

It is traditional to refer to ictal and interictal syndromes. Ictal syndromes are closely entwined with the seizure itself while the interictal syndromes are not seizure-dependent. The classic ictal

Table 21.10 Classification of psychiatric disorders of epilepsy.

Co-morbid disorders (classified after standardized manuals):
- e.g. Anxiety, depression, phobias

Integrated disorders (directly linked to epilepsy) with distinguishing features:
- Interictal dysphoric disorder (Kraepelin; Blumer)
- Interictal schizophrenia-like psychoses (Slater)
- Postictal psychoses/states
- Interictal personality disorder (Gastaut, Geschwind)
- Forced normalization (Landolt)

Table 21.11 Risk factors for interictal psychoses. From Trimble (1991).

Age of onset	Often early adolescence
Interval	Onset of seizures to onset of psychosis: approx. 14 years
Sex	F > M
Seizure type	Complex partial, often with automatisms
Seizure frequency	Diminished, especially temporal lobe
Seizure focus	Temporal, especially left-sided
Neurological findings	Sometimes sinistrality
Pathology	Gangliogliomas, hamartomas

syndromes include a pre-ictal dysphoria, the aura – particularly with a seizure focus in a temporal lobe – which can cause psychological phenomena such as *déjà vu* or depersonalization episodes and the postictal delirium. The latter rarely last more than half an hour although sometimes longer, especially in those with learning disability. Postictal delirium is an organic brain syndrome associated with considerable confusion but one from which the patient usually recovers completely and comes to no harm.

Ictal status epilepticus, particularly arising from a focus in the temporal lobes, can lead to a psychotic presentation resembling schizophrenia, although close examination will often reveal some minor and fluctuating clouding of consciousness. The EEG will almost certainly indicate the diagnosis.

Postictal psychosis should be viewed as a separate syndrome. Classically, this erupts some 24–48 hours after a cluster of seizures. The patient has a seizure cluster or a seizure that is unusual for them such as a prolonged generalized tonic–clonic attack. There is then a lucid interval between the expression of the seizures and onset of the psychosis. During this period, the patient is often quieter than usual, then some warning signs of the impending psychosis may emerge such as irritability, restlessness, sleeplessness or emotional lability.

The psychosis can come quite suddenly and is often paranoid in nature. Hallucinations and delusions are common of a schizophrenia-like nature. Many are religious in content and it is during this phase of the psychosis that patients are in danger of harming themselves. Fear of impending death is another often reported symptom. Some 50% of patients in a postictal psychosis have clear consciousness (in contrast to the postictal delirium) and can therefore plan and work out elaborate acts. Because their hallucinations are often command hallucinations and may demand either self-injury or injury to others, they are able to carry such instructions forward. Clearly, this can be a medical emergency. It is recognized that suicide is increased in people with epilepsy, particularly temporal lobe epilepsy (with estimates of up to 25 times that of the normal population) and it is during postictal states that the risk is probably at its highest. These postictal psychoses last from hours to days and may be recurrent. Approximately 25% of patients who have postictal psychoses will eventually to develop an interictal psychotic state.

Variants of the postictal psychopathology that do not reach levels of psychoses are seen with postictal anxiety states or postictal depressive syndromes. These are far more common but often not noted or even enquired about. They have a constancy of presentation and phenomenology that suggests that they are intimately linked with the seizure process, rather than with some environmentally cued aetiological factor.

Interictal syndromes bound in with epilepsy vary from anxiety states through to psychoses, although certain specific syndromes need to be clarified. Thus, while people with epilepsy can easily develop a depression, either in the setting of such an unpleasant disorder or perhaps even secondary to long-term sedatives (barbiturates were a major problem in the past), a rather specific form of depression has been recognized and is referred to as the interictal dysphoric disorder (IDD). This refers to patients who have a collection of dysphoric symptoms (irritability, anergia, depressed mood, insomnia, atypical pains, anxiety and euphoria) without the prolonged melancholia of a major depressive illness. The episodes are often short-lived, lasting sometimes a matter of days. It is thought that these are interlinked with the underlying biological processes of the epilepsy. This syndrome is important to recognize because mood lability and recurrent dysphoria easily leads to discord within a family and affects quality of life.

The interictal psychoses typically have a paranoid or schizophrenia-like presentation, often including Schneiderian First Rank symptoms but with certain features which were first specified by the papers of Eliot Slater. These include the absence of a personality deterioration over time, with the maintenance of affective warmth and a tendency to depressive episodes of the IDD type. The risk factors for developing these psychoses are shown in Table 21.11. They are linked with a limbic focus, often – initially at least – stemming from the left hemisphere and are seen in patients with long-standing and refractory epilepsy. Interestingly, bipolar disorders and affective psychoses are rarely reported as interictal syndromes.

A common site of pathology of patients with chronic epilepsy is in the medial temporal structures and it is of considerable interest that schizophrenia in the absence of epilepsy has now been shown to be associated with pathology at a similar site, albeit of a different characteristic. The difference between idiopathic schizophrenia and temporal lobe epilepsy is that the pathology of schizophrenia does not seem to include hippocampal gliosis. The similarities are disorganization of neurones primarily in the hippocampus and the fact that in both syndromes the pathology is established early in life while the main manifestations appear some years later in late adolescence or early adulthood. Both syndromes present with a wide range of psychological and behavioural signs and symptoms.

The association between epilepsy and a schizophrenia-like psychosis has now been well established in a number of epidemiological studies. The lifetime prevalence is around 10% in chronic epilepsy cases. In contrast to patients with schizophrenia, however, such patients often manage well in the community, they may be married and hold down a job and often will not report psychotic symptoms, even to their physicians.

A variant of the interictal psychosis noted in those with learning disability is one of increasing cognitive deterioration and failure to continue within the lifestyle set up by relatives or long-term carers. Such patients present with an apparent deterioration of behaviour and cognition. One possible cause for this would be a progressive neurological disorder. However, careful observation, particularly in an in-patient setting, may reveal either an undisclosed partial status epilepticus or an evolving psychosis with paranoid features that are neither well elaborated nor readily evident on account of linguistic and intellectual handicaps.

Forced normalization

Forced normalization refers to the observation that certain patients develop psychiatric symptoms when their seizures come under control. Originally this phenomenon was thought to involve psychoses alone, but other behaviours are now recognized in this setting, including depression, anxiety, agitation or even occasionally the presentation of non-epileptic seizures. In children and adolescents, a hyperactivity disorder or conduct disorder can result.

The phenomenon (Landolt phenomenon) refers to the fact that the EEG normalizes during the behaviour disturbance and that as the behaviour problems resolve the EEG resorts to its abnormal configuration. Another, perhaps better term for this is paradoxical normalization. Thus, as a general rule, if behaviour deteriorates in someone with epilepsy, the EEG also deteriorates (e.g. in non-convulsive status or with an encephalopathy). However, in the Landolt phenomenon the EEG becomes paradoxically normal when behaviour is abnormal.

The phenomenon is usually seen as an acute onset disorder, often in response to the sudden switching off of seizures in a patient with chronic epilepsy with a new anticonvulsant drug. While all anticonvulsants may lead to this problem, it is seen especially commonly following prescription of benzodiaze-pines, barbiturates, ethosuximide, vigabatrin and topiramate. A common theme to these is their GABA agonism, although this is not exclusive.

Forced normalization essentially is an EEG diagnosis, but the clinical counterpart, referred to as alternative psychosis, is also seen. In other words, patients whose behaviour alternates between deterioration with control of seizures and improvement with return of seizures over a period of time. Although these may represent episodes of forced normalization, it is only possible to confirm the latter with serial EEG recordings which may not be feasible to perform.

Finally, there is a group of patients who, over years, gradually lose their seizures but in this context develop a slowly evolving psychosis which then becomes the main clinical problem. This may represent a variant of the theme. It remains relatively unrecognized, although many cases were recorded in the older literature before effective anticonvulsant therapy was available.

Personality changes

The interictal personality syndrome, sometimes referred to as the Gastaut–Geschwind syndrome, is characterized by the following features: hyper-religiosity, with deepening concern for philosophical and mystical preoccupation; disorders of sexual function (often hyposexuality); hypergraphia (with a tendency to excessive and compulsive writing); and viscosity (stickiness of thought, bradyphrenia).

The proportion of patients who develop this syndrome is unclear and it may be up to 10% of patients with temporal lobe origins for their epilepsy and difficult to control seizures. The behaviour changes are often subtle, evolving over a matter of months or years and coming to light via the patient's relatives. Distinguishing when the behaviour becomes pathological can sometimes be difficult and not all patients show all elements of the syndrome. Geschwind considered hypergraphia to be one of the most missed neurological signs in neurological practice. In order to diagnose this syndrome it is often necessary to ask patients details about their religious beliefs, practices and observances and their writing habits, e.g. asking to see their personal diaries. This is not usually done during a conventional interview, one reason for under-reporting. This syndrome is an example of an organic personality change consequent upon chronic limbic lesions.

Movement disorders

In the same way that understanding the neurobiology of epilepsy and its behavioural consequences and associated psychiatric disorders has informed many current practices in neuropsychiatry, study of the behavioural associations with movement disorders reveals a similar constellation of concepts.

Abnormalities of movement accompany all psychiatric disorders, whether this is a mild tremor of an anxiety state or the tics, mannerisms and gestures of a schizophrenic patient or catatonia. Psychopathology is intimately bound with movement. It is often easier to recognize an emotion by the movement and gestures that accompany it than with any verbal counterpart. This association also works in reverse. Thus, a number of traditionally accepted neurological movement disorders present with a high frequency of psychopathology. Examples are Huntington's disease, Parkinson's disease and Gilles de la Tourette's syndrome. As already described, the recent unravelling of the neuro-anatomy and chemistry of the basal forebrain and related striatal structures has illuminated these relationships giving, as with epilepsy, clinical observations clear neurobiological foundations. Thus, we now know that the basal ganglia are not simply associated with extrapyramidal movement disorders, they subserve emotion and some aspects of cognition. The major outputs from the limbic lobe to the limbic forebrain use ventral striatal afferents that themselves form but one of the cortical–subcortical–cortical re-entrant pathways (Chapter 2).

Parkinson's disease

Aside from intellectual impairment – so common in Parkinson's disease – about 40% of patients meet criteria for dementia and perhaps an additional 30% have more subtle cognitive impairments – the most common psychopathologies are depression and psychoses. A dysphoric mood is frequently found. Up to 50% of patients report depressive symptoms, often with some atypical features, particularly anxiety and often an absence of guilt and self-depreciation. A lesser number on evaluation, perhaps 10%, have a typical major depressive disorder. The depression does not seem to correlate well with the extent of the physical limitations. Biological associations have been noted between Parkinson's disease and depressive illness by PET scanning which reveals decreased glucose metabolism in the frontal lobes, particularly in severely depressed patients. In some patients there is a clear history of a mood disturbance before the onset of the movement disorder.

One of the main management problems is psychosis. The psychoses of idiopathic Parkinson's disease vary considerably. Often the entry to a more malignant phase is the onset of nocturnal hallucinations, associated with some confusion. The psychosis may progress to a more pervasive and consistent form or may have started with daytime simple, or sometimes complex, hallucinations. These then gradually take on a paranoid form and a full-blown delusional state emerges. Delusions of jealousy are common and the hallucinations are most commonly visual, complex and often frightening.

The psychoses are more commonly found in association with dementia with Lewy bodies and often seem to be accelerated by the anti-parkinsonian medication. Dopamine is powerfully psychotogenic. When the effectiveness of levodopa for the physical symptoms wanes, the psychosis emerges. Sometimes this follows an increase in levodopa dosage and at others the use of dopamine agonists or polytherapy. Hallucinations occur in 30%, delusions in 10% and euphoria in 10% of patients treated with all dopaminergic agents. Sometimes these occur in the absence of an obvious delirium. Occasionally they reflect excessive use of drugs by the patient in an attempt to relieve motor symptoms. The features of the dopamine dysregulation syndrome are shown in Table 21.12.

Table 21.12 Dopamine dysregulation syndrome.

Overuse of dopaminergic medication
Risk factors: male sex and young age
Increasing doses of dopaminergic drugs despite severe dyskinesia
Behavioural and mood changes:
- Hypomania and mania
- Irritability and aggression
- Paranoia
- Repetitive purposeless motor acts (punding)
- Walking aimlessly
- Pathological gambling
- Drug hoarding
- Hypersexuality

The development of psychosis in Parkinson's disease often heralds a breakdown in community care, tolerant relatives no longer being able to accept the wayward thoughts and actions of the patient. The management is complicated because dopamine antagonists, the mainstay of treatment for psychoses, tend to make the motor symptoms worse.

Parkinsonism, as opposed to Parkinson's disease, is a not an uncommon secondary problem in people with psychoses who are treated with neuroleptic agents. Some degree of akinesia is common in such situations, but more florid presentations with typical parkinsonian rigidity and tremor is still often noted. With the advent of the atypical antipsychotic drugs the more florid manifestations of tardive dystonia and dyskinesia are now less commonly seen. Nonetheless, balancing the patient on the fine edge between mobility and psychosis represents a considerable clinical challenge.

Other movement disorders

Progressive supranuclear palsy often presents with a dementia with subcortical features. Depression and obsessive-compulsive disorder are often described in these patients.

In Huntington's disease (HD), a variety of psychopathologies may be seen, to some extent independent of the progression of the subcortical dementia. Personality changes are ubiquitous and include irritability, disinhibition, conduct disorder, antisocial behaviour and often drug or alcohol dependency. The early symptoms include emotional lability and increased excitability. Relatives complain that the person becomes more and more difficult to live with. Irresponsible and promiscuous behaviour may be reported. Loss of interest in work and the family ensues.

Depression occurs in 40–50% of HD patients, often with psychotic features. A manic presentation occurs in about 2%. Suicide is a major complication of the depression and can occur in the absence of knowledge of the diagnosis.

Psychosis occurs in 5–15% of HD patients and is typically paranoid rather than schizophrenia-like, and may precede the onset of the chorea in perhaps one-third of cases. There is no clear relationship between the expression of the abnormal movements and the severity of the psychosis. Other forms of chorea that are particularly relevant for neuropsychiatry include Sydenham's chorea and the paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). Sydenham's chorea has been associated with the development of an obsessive-compulsive disorder, while PANDAS is characterized by tics and obsessive-compulsive disorder. Affective disturbances and behaviour abnormalities are reported and patients sometimes appear hypomanic.

Gilles de la Tourette's syndrome is characterized by the onset of body and vocal tics usually in or before teenage years. The symptoms characteristically wax and wane over the years. However, tics are not just simple tics but also involve a host of complex tics, often with tortuous motor rituals. The latter can lead on to secondary neurological damage, such as repetitive neck tics causing cervical spine damage, root lesions and myelopathy.

The vocal tics are characteristic and necessary to clinch the diagnosis. Coprolalia occurs in some 30% of patients. Secondary forms of this disorder can be seen following stroke, the prescription of various stimulant drugs or after withdrawal from neuroleptics. Similar problems have also been described rarely with lamotrigine.

There are three main co-morbid neuropsychiatric disorders with Gilles de la Tourette's. In childhood, attention deficit hyperactivity disorder (ADHD) is common, occurring in about 50% of patients and at such an age can lead to severe management problems, not the least being difficulties in the home environment and with education. Obsessive-compulsive disorder (OCD) occurs in some 30–40% of patients. This can emerge during childhood but is more common in the teenage and adult years. The presentations are not typical for OCD. For example, handwashing rituals and phobias of contamination are not common. Arithmomania (a strong need to count actions or objects), sadistic and sexual obsessional thoughts are seen. The third problem is self-mutilation which has a compulsive nature to it. Some 30–40% of patients have self-mutilation in various forms, from simple cigarette burning or body punching to the more disturbing eye-poking. The desire to touch, particularly sexual parts of others, is quite often a forensic problem in these patients and the vocalizations can be so disturbing that the patient becomes socially reclusive. It is interesting that OCD and Gilles de la Tourette's syndrome appear to be inherited in an autosomal dominant fashion. Some members of the family have OCD, some Gilles de la Tourette's syndrome and others aspects of both conditions.

Other basal ganglia disorders sometimes associated with psychoses include idiopathic calcification of the basal ganglia and metabolic disorders such as hypoparathyroidism with excessive calcium deposition in these structures. Patients with Wilson's disease are not particularly liable to psychotic breakdown but do display episodes of bizarre behaviour with periods of dystonia or posturing which may last for hours at a time. The earliest psychiatric manifestations are increased restlessness but with progression of the disorder lability of affect, euphoria and obvious personality changes are seen. Cognitive impairment develops as the years go by.

White matter disorders

While so many neuropsychiatric disorders reflect on disturbed neuronal and glial functioning, it is often forgotten that disorders of white matter also can provoke psychopathology. The classic disorder is multiple sclerosis but acquired disorders of white matter and leucoencephalopathies also present clinically as behaviour problems.

In multiple sclerosis, the main neuropsychiatric problem is disturbed cognition which occurs early on in the course of the disease. This is often unrecognized, but the thinking of patients becomes more rigid and inflexible, memory complaints occur and an alteration of mood may become apparent. Often the latter is a depressive-like syndrome but with organic overtones. Fatigue is common as are emotional lability and suicidal ideation. The estimated lifetime prevalence for a major depression is about 40%. Occasionally onset of a relapse or even the first clinical episode of the disorder is an acute psychiatric presentation.

A mental state consisting of euphoria and eutonia (a sense of bodily well-being) was described earlier as rather specific for multiple sclerosis. While this picture is noted, it is essentially associated with a combination of intellectual decline and cerebral pathology particularly with multiple peri-ventricular plaques seen on MRI and cerebral atrophy. This leads to disconnection between the frontal lobes and subcortical structures and in association with the cognitive changes, denial of the severity of the illness. Interestingly, in contrast to grey matter disorders, psychoses are quite rare in multiple sclerosis. When they occur, they tend to be associated with plaques around the temporal horns of the lateral ventricles.

Treatments for multiple sclerosis may be associated themselves with psychopathology, depression being a particularly common side-effect of beta-interferon. Suicide is an ever present risk and any threat to self-harm should be taken seriously.

Patchy deep white matter lesions are often seen on MR T2W scans and are in many settings apparently of little clinical significance. However, it has been shown that there is an increased risk of depression with such scan abnormalities when they are florid. The depression tends to occur more after the age of 50 and it is often quite treatment-resistant. Again, changes in relation to frontal basal ganglia circuitry are most often linked with the psychopathology.

Another syndrome of myelin destruction, subacute combined degeneration secondary to vitamin B_{12} depletion is rarely seen these days, but B_{12} deficiency can present with anything from mild forgetfulness and irritability to psychoses, confusional states and dementia. Folate deficiency has for a long time been linked with depression and occasionally a patient is found with intractable depression who responds to folic acid.

Central pontine myelinolysis is a rare disorder but which can occur following alcoholism with states of malnutrition, especially with electrolyte imbalance and hyponatrenia if this is rapidly reversed. Subtle changes of the mental state including a pseudobulbar palsy may be seen and in dilapidated patients this presentation may accompany a Wernicke–Korsakoff encephalopathy (Chapter 18).

One of the challenges of neuropsychiatry is the identification of genetic disorders affecting white matter which in childhood present with severe neurological symptomatology and often early death. In variants that affect patients in teenage years or early adulthood, there is often an initial presentation with florid psychiatric problems. At first these may be rather non-specific, but they soon progress to overt cognitive dysfunction with loss of behavioural control and ultimately to a psychotic state. A typical example is metachromatic leucodystrophy: patients with juvenile and adult onset forms presenting with personality changes and dementia and a schizophrenia-like illness.

In adrenoleucodystrophy, dementia, learning difficulties and behaviour changes are the most frequent presenting psychiatric problems but again schizophrenia-like states have been reported. Homocystinaemia can present with cognitive impairment and behavioural change. There are a number of glycogen storage disorders that present with psychiatric symptomatology as the age of the patient increases. Most are inherited as autosomal recessive or X-linked conditions and many reveal the CNS symptoms as part of a more generalized metabolic problem. Psychoses are reported in association with subacute sclerosing panencephalitis and with tuberous sclerosis, in the latter usually associated with accompanying epilepsy. The psychoses are schizophrenia-like, patients having good affective responsivity and little deterioration over time, with unusual auditory hallucinations of a constant nature, e.g. the reported hearing of a favourite rock band.

The term 'progressive disintegrative psychosis' is sometime used to distinguish these psychotic presentations from, for example, childhood autism, where the behaviour abnormality characterized by disturbances of language and an inability to form normal interpersonal relationships is recognized from early childhood. The hallmark is progression of the psychopathology, out of proportion to any suggested environmental stress, leading to the frank psychotic disorder. In the non-progressive disintegrative psychoses, there is normal development for the first few years of life with a subsequent loss of skills, but no progressive disintegration. Examples are Heller's syndrome, or in epilepsy the Landau–Kleffner syndrome.

Other interesting neuropsychiatric disorders

Many neuropsychiatric presentations can be understood as a consequence of disorders of the limbic-related motivational–motor neuro-anatomical interface. However, particularly in the 19th and early 20th century, neuropsychiatry was involved in the identification of neocortical focal signature syndromes. Some of these are covered in other chapters of this book, but classically alterations of behaviour involve frontal and temporal cortical circuitry disorders and much has been written about the neuropsychiatry of frontal lobe syndromes. Because the frontal lobes comprise almost one-third of the cortical surface area, complete myelination late in early to mid adult life, and have intimate connections with limbic and the posterior sensory association cortices, they are anatomically poised, both to integrate environmental and emotional information and to formulate and to execute motor action plans. Hence their relationship to so-called executive function and to a number of behavioural syndromes. It may be asserted that any psychiatric disorder includes aspects of a frontal lobe syndrome.

There is much mythology about these syndromes and some of this has been driven by the identification of frontal lobe dysfunction using neuropsychological test batteries. However, the validity and reliability of these are still unclear. More importantly, many patients with psychopathology have been shown to have disturbed frontal functioning as a feature of their psychopathology. The ubiquitous nature of frontal activity with such extensive cortical and subcortical connectivity means that failure to perform as expected on these so called frontal-executive tasks is quite non-specific. Central executive systems are not modular and localized, and the so-called frontal lobe tests do not therefore necessarily test activity only of the frontal lobes. Frontal task-solving problems are impaired in patients with schizophrenia, depressive illness and obsessive-compulsive disorder. Further, patients with personality disorders, e.g. borderline personality disorder, also have frontal lobe dysfunctions when tested on neuropsychological batteries. Any person with limited intellectual abilities will also have difficulty performing such tasks. It is for these reasons that apparent frontal lobe dysfunction based purely on neuropsychological test findings cannot be a valid indicator of frontal lobe damage.

Other signature syndromes that often involve the neuropsychiatric assessment include some aphasic syndromes and the right hemisphere syndrome. The confusion of a fluent aphasia (Wernicke's) punctuated with neologisms can occasionally be mistaken for a schizophasia, but close evaluation will reveal the associated neurological impairments or the underlying nature of the paranoid delusions in schizophrenia. Aprosodias, in which the melodic and intonational aspects of speech are lost, occur following non-dominant hemisphere lesions in the equivalent areas that deal with language in the left hemisphere. Gesture is usually reduced in patients with dysprosody and such patients often have considerable difficulty communicating their feelings, leading to an under-estimation of their distress. The angular gyrus syndrome following lesions of the left angular gyrus produces agraphia, acalculia, right–left disorientation and finger agnosia (Gerstmann's syndrome) with, in addition, constructional disturbances, apraxia and alexia and memory problems. The clinical picture can be so confusing that it is easily mistaken for Alzheimer's disease or for a non-neurologically based pseudodementia.

Neuropsychiatric syndromes following right hemisphere dysfunction are often unrecognized. If a patient has a left hemisphere stroke, the resulting aphasia will lead to an instant referral to neurology. However, non-dominant hemisphere lesions often present with psychopathology and the neurological underpinnings of their problem missed. Apathy and sometimes abulia result, which are often misinterpreted as a depression. Secondary manias occur following lesions of the orbitofrontal cortex–basal ganglia circuitry. Depression is most frequently associated with right posterior cortical lesions while delusions may arise with lesions of the right temporal lobe or temporoparietal junction. Misidentification syndromes, such as the Capgras syndrome, are more common with right-sided lesions.

The psychiatric syndromes, particularly psychoses and depressions, following right hemisphere insults are difficult to treat and have a poor prognosis. A table of neuropsychiatric syndromes reported in patients with right brain lesions is given in Table 21.13.

Table 21.13 Right hemisphere psychiatric syndromes. From Cummings & Trimble (2002).

Syndrome	Lesion location
Depression	Frontal lobe, temporal lobe, caudate nucleus
Depression with anxiety	Frontal cortex
Psychosis	Temporal lobe
Visual hallucinations	Geniculocalcarine radiation, occipital cortex, temporal lobe
Apraxia	Parietal lobe, frontal lobe, corpus callosum
Primary acalculia	Parietal lobe
Verbal amnesia	Temporal lobe
Spatial neglect	Parietal lobe
Denial of language deficit	Temporoparietal region

Table 21.14 Aetiological factors in psychiatric disturbance after head injury. After Lishman (1998).

Mental constitution
Premorbid personality
Emotional impact of the injury
Emotional repercussions of the injury
Environmental factors
Compensation and litigation
Response to intellectual impairments
Epilepsy
Extent of brain damage
Location of brain damage
History of substance abuse

Psychogenic amnesias

Memory disorders are discussed elsewhere within this book. However, so much is written about the structural basis of memory disorders, linked with hippocampal circuitry, that the dynamic and autobiographical nature of our memory is overlooked. In many languages 'to remember' is expressed reflexively (German: *ich erinnere mich*). The brain recalls things past; remembering is a creative form of forgetting. What is represented in our memory and how it is represented is entirely elusive and illusive.

Psychogenic amnesia is also referred to as dissociative amnesia. Essentially this refers to an episode of inability to recall important personal information, usually related to traumatic or stressful events. There is preservation of the ability to comprehend environmental information and to perform complex learned skills. However, psychogenic amnesia may occur in the setting of subtle neurological illness, particularly following minor head injury. Situational psychogenic amnesias occur in association with psychologically traumatic events and may form part of a larger clinical picture of a post-traumatic stress disorder, with psychological intrusions, increased arousal or the development of phobias or fugue states.

The Ganser syndrome is a complex of hallucinations, cognitive disorientation, some conversion symptoms and the symptom of approximate answers (*Vorbeireden*). It has been described in a number of settings and has been associated with head injury, depression, schizophrenia, and epilepsy, but it is also noted in malingering. *Vorbeireden* is the inability to answer simple questions correctly even though the nature of the question is known: approximate answers are given.

Pseudodementia is an all-embracing term for cognitive and memory impairments that are seen in a variety of settings from depression through to schizophrenia and in some people with early onset dementia who present with a catastrophic loss of memory and other cognitive abilities. Embraced under this term is also the Ganser syndrome and hysterical dementia. Patients with the latter have a bizarre memory loss, associated with variable and inconsistent results on neuropsychological testing but often seen in conjunction with other conversion phenomena. The memory loss may be acute or chronic but is out of keeping with the patient's observed abilities in everyday life. The condition may be precipitated by a minor head injury and in a compensation setting often leads to the suspicion of malingering.

Reduplicative paramnesia is a syndrome in which a patient is certain that a familiar place, person, object or body part has been duplicated. For example, the patient will insist that a familiar place (the hospital room) exists in an impossible location, e.g. in their house. It is usually discussed in the context of a misidentification syndrome.

Post-concussional syndrome

The nosological status of this condition is always in doubt. It is often reported in patients who have minor head injuries. They complain of headache, dizziness, diplopia, fatigue, noise sensitivity and poor concentration. Normally, patients recover within a few weeks but there is a small percentage who remain symptomatic in the long term. In some patients there may be subtle signs of damage noted on brain imaging or with abnormal vestibular tests, but it should be noted that similar symptoms are reported in people involved in accidents with bodily trauma who have no head injury. However, the symptoms can blend in with those of anxiety, depression and post-traumatic stress disorder. It is generally accepted that the longer the symptoms go on the less likely they are to be caused by any underlying neurological impairment. It is often forgotten that the head holds a special place in the personal concept of the body image and head injury, of whatever severity, poses a threat that injury to other parts of the body usually does not. In addition, head injury often is the result of an accident and someone else may well be to blame or it can be related to some complicated psychosocial setting leading to unresolved conflict or guilt. In these settings psychological factors are most likely to be predominant in determining symptoms. Some of the aetiological factors of psychiatric disturbance following head injury are shown in Table 21.14.

Treatments

Drug treatments

This is not the correct setting to describe in any detail the use of psychotropic drugs for psychiatric disorders secondary to neurological diseases. However, a few comments of clinical relevance should be made, and some of the neurological consequences of psychiatric treatments noted.

In general, psychotropic medication should be started with low doses and built up to effective ones, and they should never be stopped suddenly. Some of them have dependence potential (e.g. benzodiazepines), while others, such as antidepressants and antipsychotics, do not. However, reassuring patients that they will not develop a dependency is often important in management, because such is a frequently expressed fear.

All of the psychotropic drugs are neuromodulators and there is of necessity overlap between the use of many of these drugs in neurology and psychiatry. The main target neurotransmitters are dopamine, noradrenaline, serotonin, GABA and glutamate. A classification is given in Table 21.15.

With regards to antidepressants, there are the monoamine oxidase inhibitors (MAOIs) and tricyclic drugs but selective serotonin re-uptake inhibitors (SSRIs) are most popular. There are a number of variants available, including drugs such as venlafaxine and duloxetine, serotonin–noradrenaline re-uptake inhibitors, and mirtazapine, a noradrenergic but selective serotonergic antidepressant. Their main advantages are the lack of cardiac effects and therefore safety in overdose and lack of sedation. They are best given in daytime doses. Side effects of non-MAOI antidepressants are shown in Table 21.16, some of which obviously have neurological significance including tremor, dyskinesias and myopathy. The SSRIs can cause extrapyramidal disorders including akathisia and dystonia.

Seizures can be precipitated. These are more common with certain antidepressants of which maprotiline, mianserin, clomipramine and buproprion are representative. The risk of an increase in seizures in epilepsy, however, needs always to be mentioned, but this is not usually a problem in clinical practice, partly because patients with epilepsy are on antiepileptic drugs and partly because patients most susceptible to depression are often those with refractory epilepsy, who already have quite frequent seizures. In some patients, who respond to the psychotropics but who do experience an exacerbation of seizures, a judicious increase in the antiepileptic drug therapy may be warranted.

The problem is the more difficult patient who has been seizure free for a long time, but who develops a psychiatric disorder requiring treatment. Such patients are susceptible to the provocation of a seizure, either on account of the pro-convulsant potential of the drugs or because of a pharmacokinetic interaction. Careful discussion of the possibility of a seizure with the patient is mandatory.

Pharmacokinetic interaction possibilities are legion. Most psychotropic drugs utilize the CYP 450 enzyme system. For details of specific interactions the reader is referred to recent reviews. However, in clinical practice the main problems are the lowering of levels of the psychotropic drugs by enzyme inducers, such as anticonvulsants and the provocation of anticonvulsant toxicity with some antidepressants, especially fluoxetine and citalopram. If there is concern about possible interactions, then serum levels of anticonvulsants should be taken before the administration of the psychotropic for later comparison and any deterioration of behaviour checked against repeated serum level assessments.

Table 21.15 Classification of psychotropic drugs.

Antidepressants
Monoamine oxidase inhibitors (MAOIs)
Moclobemide, phenelzine

Tricyclic antidepressants (TCAs)
Amitriptyline, nortriptyline, clomipramine, imipramine, desipramine, maprotiline

Tetracyclic antidepressants
Mianserin

Selective serotonin re-uptake inhibitors (SSRIs)
Fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram

Noradrenergic uptake inhibitors (NARIs)
Reboxetine

Noradrenaline–serotonin uptake inhibitors (NSRIs)
Venlafaxine, duloxetine

Noradrenaline–selective serotonin antidepressants (NASSAs)
Mirtazapine

Serotonin antagonist and re-uptake inhibitors (SARIs)
Trazodone, nefazodone

Antipsychotics
Typical
Phenothiazines, e.g. thioridazine, mesoridazine, chlorpromazine, prochlorperazine
Butyrophenones, e.g. haloperidol

Atypical
Benzioxazoles and benzisothiazoles, e.g. risperidone, ziprasidone, perospirone
Thienobenzodiazepine, dibenzothiazepine and dibenzothiazepine derivatives, e.g. clozapine, olanzapine, quetiapine

Others
Sulpiride, amisulpiride

Minor tranquillizers
Barbiturates, benzodiazepines, others

Mood stabilizers
Lithium carbonate, valproic acid, carbamazepine, lamotrigine

Others
Beta-blockers, amfebutamone (bupoprion)

Antidepressants need to be given for at least 6 months in a patient who has developed a major depressive disorder, but variants, such as the interictal dysphoric disorder of epilepsy, may

Table 21.16 Side effects of non-MAOI antidepressant drugs.

Sedation
Dry mouth
Palpitations and tachycardia
ECG changes
Visual difficulties
Postural difficulties
Postural hypotension
Nausea, vomiting, heartburn
Constipation
Glaucoma
Urinary retention, impotence, delayed ejaculation
Paralytic ileus
Galactorrhoea
Sweating
Fever
Tremor
Dyskinesia
Myopathy, neuropathy
Convulsions
Ataxia
Delirium
Agitation
Transient hypomania
Depersonalization
Aggression
Jaundice (cholestatic)
Weight gain
Impairment of cognitive function
Rashes
Extrapyramidal reactions

resolve without therapy after a few days, although they may become repetitive and persistent requiring longer term mood stabilization.

The antipsychotics include two large groups: typical and atypical. The former group divide into the phenothiazines (such as chlorpromazine), the butyrophenones (such as haloperidol) and others. The atypical drugs have become more popular recently and include sulpiride, risperidone, olanzapine, quetiapine, amisulpiride and clozapine. While all neuroleptics that are antipsychotic block dopamine receptors, the atypical drugs preferentially act on dopamine receptors outside the dorsal striatum, which leads to much less of a tendency to provoke extrapyramidal problems. The atypical antipsychotic drugs also have a greater affinity for antagonism of cortical 5-HT2 receptors, thought to be important in their antipsychotic action. Again there are metabolic interactions through the CYP 450 system, but these are less with the newer generation of drugs. Enzyme-inducing drugs will lower the serum levels of some, and possibly therefore their effectiveness.

Traditional antipsychotics have long been recognized as a class of drugs that can increase the risk of seizures. To determine the risk for drug-induced seizures, different approaches have been adopted: observational studies (case–control studies and case reports), drug-induced EEG changes, animal models and *in vitro* techniques in isolated tissue samples. One of the problems of the recent literature is that most of the studies have been performed on psychiatric patients and it is not known whether drug-related seizures in non-epileptic patients really predict risk in patients with epilepsy or whether different neurological syndromes have different risks for psychotropic-induced seizures. Patients with a prior history of head injury and stroke may be at increased risk.

Generally, chlorpromazine and clozapine are considered pro-convulsant, the former only at high doses (1000 mg/day) and the latter at medium and high doses (>600 mg/day). Clozapine frequently causes epileptiform EEG changes and seizures in 3–5% of patients treated, even at therapeutic doses. The EEG changes may be recorded at low doses and the seizures are often myoclonic, but can be generalized tonic–clonic or partial.

Olanzapine is structurally related to clozapine; it is in the thienobenzodiazepine class of atypical antipsychotics and, along with quetiapine, premarketing studies showed a low seizure rate of seizure provocation. It should be noted that studies of the frequency of seizures have been gathered from patients with psychiatric disorders and not on patients with neurological disorders. However, some cross-generalizations may be expected; for example, there is little reason to believe that a drug that is pro-convulsant in psychiatric populations will not also be pro-convulsant in people with epilepsy or other disorders that lower the seizure threshold.

Finally, the special role of clozapine in the psychoses of neurological patients should be noted. This drug may seem contraindicated in patients with epilepsy, especially on account of its pro-convulsant liability. However, it has been used successfully in the management of the interictal psychoses of epilepsy with certain provisions. It is a remarkably useful antipsychotic in patients whose psychosis fails to respond to other atypical antipsychotics. The use of clozapine is most successful when given to a patient who has developed a psychosis and become seizure free, suggesting some variant of the theme of forced normalization, requiring perhaps a more pro-convulsant antipsychotic for a clinical effect. It is also used in the management of psychoses in Parkinson's disease where, in small doses, it will control a psychosis without leading to deterioration of the motor disorder. Atypical antipsychotics are also used in the management of Huntington's disease, states of delirium, Gilles de la Tourette's syndrome and in the control of mood.

The side effects of drooling and weight gain are problems with the use of clozapine, and it should not be used in patients who are taking carbamazepine. However, a change of the latter to oxcarbazepine is an acceptable clinical manoeuvre. A complication of clozapine and some other atypical drugs is development of a metabolic syndrome – increased weight, high cholesterol and Type 2 diabetes. In epilepsy, an EEG should be performed before administration of clozapine, in case of a deterioration of behaviour, so that development of a non-convulsive status epilepticus can be identified and managed. Clozapine should be introduced slowly, white cell counts monitored and increased in doses up to 300–600 mg/day, although some patients respond to lower doses.

Extrapyramidal side effects were a problem with the typical antipsychotic drugs and included a spectrum from acute akinesia, akathisia, dystonias and parkinsonism, to chronic variants such as tardive dyskinesias, the rabbit syndrome (oral pouting/sniffing), dystonias, parkinsonism and Gilles de la Tourette's syndrome. However, higher doses of atypicals such as risperidone do lead to extrapyramidal signs. The neuroleptic malignant syndrome remains a low but present risk, even with clozapine.

With regards to the sedative drugs, barbiturates are rarely used nowadays, the main medications being benzodiazepines, which have tranquilizing, anticonvulsant and muscle relaxant properties. However, some of them are also quite amnestic. Their side effects

Table 21.17 Toxic effects of lithium.

Neuropsychiatric	Drowsiness
	Confusion
	Psychomotor retardation
	Restlessness
	Stupor
	Headache
	Weakness
	Tremor
	Ataxia
	Myasthenia gravis-like fatiguability
	Peripheral neuropathy
	Choreoathetoid movements
	Cerebellar syndrome
	Dysarthria
	Dysgeusia
	Blurred vision
	Seizures
	Dizziness, vertigo
	Impaired short-term memory and concentration
Gastrointestinal	Anorexia, nausea, vomiting
	Diarrhoea
	Dry mouth, metallic taste
	Weight gain
Renal	Microtubular lesions
	Impairment of renal concentrating capacity
Cardiovascular	Low blood pressure
	ECG changes
Endocrine	Myxoedema
	Hyperthyroidism
	Hyperparathyroidism
Other	Polyuria and polydipsia
	Glycosuria
	Hypercalcinuria
	Rashes

include withdrawal seizures, but also a return of acute anxiety on too rapid withdrawal. Concentration and memory problems occur not uncommonly especially in the elderly, and also ataxia.

Considerable interest has been shown recently in mood stabilizers; the classic prescription is lithium. Many patients cannot tolerate this and it has a considerable number of neuropsychiatric side effects. These are shown in Table 21.17. Seizures are most common when plasma levels exceed 3.0 mEq/L. At therapeutic levels, the effect of lithium on seizure frequency in individuals with epilepsy is inconsistent and unpredictable. Thus, although reports are conflicting, it appears that lithium can be prescribed safely in patients with epilepsy when mood-stabilizing therapy is necessary and alternative agents either fail or are not tolerated. In these situations, vigilant monitoring of lithium blood levels and clinical signs of neurotoxicity is important.

Lithium carbonate is frequently used for manic episodes in bipolar disorder and for the long-term prophylaxis of unstable mood. Other drugs in use with proven efficacy for the latter are carbamazepine, valproic acid and lamotrigine. Carbamazepine can increase the incidence of lithium toxicity and alters several hematological parameters (mainly leucocyte count). It also causes a significant modification in thyroid function with a decrease in T4 and free T4. The opposing effects of carbamazepine and lithium on electrolyte regulation are well known, with the potential occurrence of severe hyponatremia when lithium alone is stopped.

The combination of lithium and valproic acid is widely used in rapid cycling, manic, depressive and mixed episode bipolar disorder. This combination seems to have a higher tolerability than the co-administration with carbamazepine and a pharmacodynamic synergistic interaction has been suggested. However, the combination of lithium and valproic acid may induce additive side effects, such as weight gain, sedation and tremor.

Some of the side-effects of lithium can be avoided by regular monitoring of serum levels, but polyuria and polydipsia can be troublesome and occasionally a picture of nephrogenic diabetes insipidus can be seen. Severe intoxication may lead to an encephalopathy and may present with hyperactive reflexes, tremor, seizures and focal signs.

The anticonvulsant drugs (Chapter 6) may provoke psychopathology in patients with epilepsy, in part through their sedative action and in part on account of their neurochemical action and the phenomenon of forced normalization. It is the case that not all anticonvulsants are mood stabilizing and their spectrum of positive and negative effects on mood has helped unravel the underlying neurochemistry of mood instability – another aspect of neuropsychiatry.

The precipitation of an acute psychiatric disorder, sometimes with psychotic features, by anticonvulsant medications as seizures are suddenly switched off (forced normalization) has already been discussed.

ECT, ablative surgery and neurostimulation

Electroconvulsive therapy (ECT) is still used in some centres and is valuable in patients with an acute or chronic depressive illness of severity that has not responded to conventional medications. The main indication is mood disorder, especially delusional states, but it has been shown to be helpful in catatonia (where it is the treatment of choice) and in Parkinson's disease to help both depression and the motor disorder. Very occasionally, ECT has been shown to help resolve epilepsia partialis continua. Contraindications are few but it is best avoided if possible following a recent stroke or in the presence of any condition where there may be raised intracranial pressure.

Vagus nerve stimulation has become popular for the treatment of epilepsy in recent years; it appears in epilepsy to have some beneficial effects on mood and has now been introduced into clinical practice for the treatment of chronic resistant depression. It is one of a growing number of techniques that are becoming available for alteration of brain function by stimulation. Transcranial magnetic stimulation is also used in some centres, and is an evolving method of treatment for depression. Neurosurgical procedures for psychiatric disorder have been used frequently in the past, e.g. various frontal leucotomies. Operations included orbital undercutting and capsulotomy, the main anatomical circuits interrupted by such surgery being fronto-thalamic. These procedures traditionally worked best in patients with chronic remitting depressive illnesses, with good premorbid personalities and with severe obsessive-compulsive disorder. The introduction of stereotactic techniques has rendered such procedures much safer, but all ablative procedures are now rarely performed for psychiatric illness. Deep brain stimulation has, however, ushered in a new era of surgical treatment.

Psychological treatments

Psychological intervention in neurological practice has increased considerably in recent years, not only in the management of somatoform disorders but also in dealing with the psychiatric co-morbidities of patients with diseases such as stroke, epilepsy and Parkinson's disease. The available treatments vary from prolonged and intensive psychodynamic psychotherapy (e.g. in the borderline patient with non-epileptic seizures) to the widely used and brief cognitive behavioural therapy that is symptom targeted. These treatments have been shown to be particularly valuable in the management of non-epileptic seizures with a predominantly anxiety-related basis. They are also used in settings where self-confidence has collapsed, such as in patients who are dizzy, elderly patients with falls and patients with epilepsy who have become increasingly fearful of having seizures in public. Psychological education and social skills training may also benefit patients with a wide variety of neurological conditions: the skills of specialist nurses in movement disorder, epilepsy, stroke and multiple sclerosis clinics have provided important additions to management.

Additional therapies that have become available using psychological mechanisms include biofeedback: patients autogenically change their own physiological activity in response to sensory biofeedback. Such techniques have been used to help neurological conditions from migraine through to epileptic seizures.

While in the past the introduction of psychological perspectives into neurological practice was often considered inappropriate and intrusive, recently psychological interventions have become widely accepted far beyond the field of psychiatry.

Conclusions

Neuropsychiatry is an old discipline with a long and distinguished history. The first neuropsychiatrist at the National Hospital was Dr John Hughlings Jackson (1835–1911) whose elegant theories relating brain function to structure still deserve careful consideration. The intellectually dishonest break between neurology and psychiatry which involved the first 60 or so years of the 20th century has been surpassed by huge advances in the neurosciences, aided much by inventive techniques of investigating the brain unavailable to earlier generations. Behavioural neurology and neuropsychiatry are now well represented conceptually and have become specialties in their own right. There has always been a psychiatry of neurology and a neurology of psychiatry. The artificial separation between the two disciplines has now been largely dispelled. With new neuro-anatomical and neurochemical concepts, we have a more complete understanding of clinical signs, symptoms and behaviour – for our own illumination and for the treatment of our patients.

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22 Pain

Geoffrey Schott

Usually one of three issues concerns the neurologist confronted with a patient with pain. Does the pain have an underlying neurological cause? What part does pain play in a patient's neurological condition? How should the pain be managed? This chapter deals with these issues and discusses some of the underlying mechanisms. The last issue, the management of difficult chronic pain, is often more the concern of colleagues in multidisciplinary pain management.

Despite being a subject of interest to only a minority of neurologists, pain is a phenomenon that nevertheless shows numerous features reflecting fascinating and sometimes unexpected aspects of the nervous system. Furthermore, even seemingly straightforward issues are now known to be far more complex, as illustrated by some examples:

- The subjective nature of pain. Whilst numerous pain scales and other measuring tools have been devised, both for adults and children, chronic pain is a novel experience for the individual. It is inevitably an experience which is impossible to convey with accuracy and for which words fail, making both clinical practice and research difficult and often imprecise.
- The sensory and emotional components of pain. The complex and probably ever-present relationship between the sensory and the emotional and affective components intrinsic to the experience of pain is being increasingly recognized. Appreciating the twin components has major implications for theory and practice.
- Peripheral versus central pains. The customary division of the nervous system into the peripheral and central nervous components is often unhelpful. A number of disorders such as shingles and brachial plexus avulsion injuries may affect both divisions; every peripheral pain is associated with ascending and descending cascades of central physiological and neurochemical changes affecting the spinal cord and brain; and central lesions of the nervous system often result in peripheral disturbances.
- The specificity of pain-subserving pathways. On the one hand, simple notions of pain pathways that resemble tramlines may have been thoroughly overturned. On the other hand, selective lesioning of the spinal cord by anterolateral cordotomy can abolish pain sometimes for long periods, and pain resulting from a stroke can be abolished by a second small stroke – facts arguing for selective anatomical pathways mediating pain.
- Stimulation of the nervous system for pain relief. This concept is counter-intuitive when treating symptoms that are by definition already positive and excessive. Nevertheless, numerous stimulation techniques have been explored, and sometimes one or more of them may prove valuable in pain management.
- The relationship between pain and itch. Both are unpleasant sensory experiences, are subserved by C fibres, project to the brain through the anterolateral quadrant of the spinal cord, and can be caused by the same neurological disorders including shingles, thoracic root compression, multiple sclerosis, brain tumours and stroke. In some of these conditions pain and itch can coexist. However, pain and itch tend to inhibit each other, and are also clearly different in the types of sensation and behavioural responses induced, the population of C fibres and ascending tracts involved, and possibly the types of cerebral processing.

The terminology and classification of pain

The International Association for the Study of Pain (IASP) has defined pain as 'An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.' Such a definition is at best an approximation, and, particularly in the case of neuropathic pain, which will be a novel phenomenon for the sufferer, the limitations of description are obvious. This is especially so in respect of those unable to express themselves, such as individuals who are mentally impaired, demented, aphasic or very young.

Pain may be classified as on-going (stimulus-independent) or induced (stimulus-dependent) – whether by mechanical (brushing, pinprick, pressure, movement), chemical or thermal (warmth,

Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

heat, cool and cold) stimuli. Sometimes both types of pain will be present. Whenever possible, pain should be described in terms that specify the type of pain, and it should be recalled that pinprick applied to the skin induces sharpness (mediated by Aδ fibres) unless applied sufficiently deeply and vigorously so as to produce painful tissue damage (mediated by C fibres).

Perhaps the single characteristic most suggestive of pain of neuropathic origin is a burning quality, although this burning is neither invariable, nor diagnostic. Patients also often demonstrate unusual sensory features, many of which have been given specific terms, clarified by IASP:

- *Allodynia:* pain due to a stimulus that does not normally provoke pain. There are different varieties, including mechanical, cold and heat allodynia, in which stimuli such as a light brush, cooling or warmth trigger pain. The two crucial features are the change in quality (i.e. modality) of sensation from one that is normally innocuous to one that is painful, and the lowered pain threshold. An everyday example is pain over an area of sunburn – pain is produced by gentle touch.
- *Hyperalgesia or hypoalgesia:* increased or decreased pain response to a normally and specifically painful stimulus. This is a threshold phenomenon, and, contrasting with allodynia, there is no change in modality.
- *Hyperpathia:* an abnormally painful reaction to a stimulus, which may occur with other heightened sensory states such as allodynia, hyperalgesia, hyperaesthesia and dysaesthesia. There is an increased threshold to sensory stimuli, often with other clinical phenomena, e.g. delay in response, radiation and after-sensations, and impaired identification and localization of stimuli.
- *Hyperaesthesia or hypoaesthesia:* increased or decreased sensitivity to stimulation. If pain results from innocuous stimulation, allodynia often results.
- *Dysaesthesia:* an unpleasant abnormal sensation, whether spontaneous or evoked.
- *Anaesthesia dolorosa:* pain in an anaesthetic area.

Often the most revealing signs, at least in pain of central origin, are impaired pain from pinprick and/or impaired thermal sensation – the latter sometimes detectable simply by impaired cold appreciation from skin contact with a tuning fork.

Apart from standard neurological examination and investigations, with emphasis on assessment of small nerve fibre function, more sophisticated investigations are sometimes used, particularly in research. In humans, methods for assessing peripheral mechanisms of pain include quantitative sensory testing (QST), sweat measurement, skin biopsy for assessment of intraepidermal nerve fibre density and for immunohistochemical studies, e.g. on substance P and calcitonin gene-related peptide (CGRP), and trophic factors such as nerve growth factor (NGF). Other studies include sympathetic skin responses, scintigraphy to measure plasma extravazation, and nerve, muscle and synovial biopsies. Neurophysiological techniques include microneurographic recordings from single sensory units in intact human nerves and recordings from intraneural electrical microstimulation. Methods used to study central pain processes include functional magnetic resonance imaging (MRI) and positron emission tomography (PET) studies of the brain and more recently functional MRI of the spinal cord; laser-evoked potentials to assess pain-subserving central sensory pathways; and EEG and magneto-encephalography (MEG) to study spinal and cerebral mechanisms.

Pain has been divided into two categories: nociceptive and neuropathic (neurogenic). Nociceptive pain results from lesions affecting non-neural structures, e.g. a burn, arthritis, myocardial infarction or a limb fracture. Neuropathic pain results from lesions affecting the peripheral or central nervous systems. Once again, such a division is sometimes more theoretical than real; thus, a fracture will very often also involve neural structures, and arthritis will be associated with chemical changes in and around the joint, which have major effects on the local innervation. Conversely, many patients with neurological disorders have musculoskeletal complications which are painful. There are also some conditions where non-neural and neural structures are so intimately involved that separation into nociceptive or neuropathic components becomes unhelpful. Examples are the glomus tumour of a finger and complex regional pain syndromes (reflex sympathetic dystrophy), both of which are discussed below.

Accepting the limitations of arbitrary classification, the clue that pain is primarily neuropathic is the presence of accompanying neurological signs. These signs are in particular sensory. They may include sensory loss, the various sensory phenomena defined above, other phenomena such as delayed or prolonged after-sensations following a peripheral stimulus, and faulty identification and localization of pain. There may also be radiation of both stimulus-induced and spontaneous pain, and referred pain, including mirror image pain. Such features, particularly when accompanied by non-sensory phenomena such as weakness, wasting, tremor, dystonia and other involuntary movements, indicate that the nervous system has changed in the way it processes sensory information. However, a word of caution is necessary in interpreting sensory deficits in the presence of pain: intriguingly, if pain is relieved, the sensory deficit may improve. This has been found both in experimental studies and through clinical observation; both peripheral but more particularly central mechanisms have been invoked.

Although patients with neuropathic pain may also have coexisting nociceptive pain, and evaluation of these different components is crucial, it is neuropathic pain that is mainly considered in the topics that follow.

Some painful neuropathic conditions

Central pain

The three most common causes of central pain, which share many features, comprise:

- Central post-stroke pain (CPSP);
- Multiple sclerosis;
- Spinal cord injury.

Table 22.1 Classic features of central post-stroke pain (the thalamic syndrome).

A mild, rapidly improving hemiplegia without contractures
Persistent superficial hemi-anaesthesia or hyperaesthesia, with impaired deep sensation
Mild hemi-ataxia and astereognosis
Choreo-athetotic movements on the paralysed side
'Sharp, enduring, paroxysmal, often intolerable pain on the hemiplegic side which does not respond to any analgesic treatment'

Central post-stroke pain (the thalamic syndrome)

In 1906, Dejerine and Roussy, in their seminal paper 'Le syndrome thalamique', brought to attention the pain syndrome that can follow a stroke. They reported five patients who had suffered from pain following a thalamic infarct, three of whom at postmortem had destruction predominantly affecting the posterolateral ventral thalamus, with some lateral extension. This pain syndrome comprised a number of features (Table 22.1).

Concepts surrounding CPSP have developed considerably in the past century:

- Although mechanical shoulder pain associated with hemiplegia is probably the most common type of post-stroke pain, it is now known that 8–10% of patients have central post-stroke pain a year after their stroke. Far from being a rarity as often thought, this pain syndrome is therefore common. It afflicts many thousands of patients, most of whom will be at home, with their pain often remaining unrecognized.
- Reflected in the change in terminology from thalamic pain to CPSP, the same type of pain can occur following a stroke affecting any part of the somatosensory central nervous system. The original reports were founded on clinical observations, but subsequently neuro-imaging has confirmed the numerous and sometimes non-specific potential sites from where pain can arise. Apart from the posterolateral ventral thalamus, strokes involving the medulla (particularly in the posterior inferior cerebellar artery territory – Wallenberg's syndrome) and occasionally the parietal cortex (the parietal pseudo-thalamic pain syndrome) are those most likely to cause pain. Most cerebral ischaemic lesions are due to infarcts, which may be very small, although there is no correlation between size of lesion and pain. Furthermore, when there are numerous lesions on a scan, it may be impossible to know which is the causative one.
- The same type of pain can be caused by vascular lesions other than those due to cerebral or spinal infarcts, including subarachnoid and other intracranial haemorrhage.
- Similar central pain can also result from non-vascular causes that affect the brain or spinal cord, including multiple sclerosis and spinal trauma, as well as rarer disorders such as cerebral trauma, tumours, syringomyelia and syringobulbia, infections, and iatrogenic surgical and needling procedures.

CPSP can be viewed as the prototypic central pain, and accounts for 90% of supraspinal central pain. Whatever its cause, central pain often comprises a number of similar characteristic features (Table 22.2) and various clinical findings (Table 22.3).

Table 22.2 Clinical features of central pain.

Is often very difficult for the patient to describe
Can be on-going, triggered, or a combination; superficial, deep, or a combination
Most often has a burning quality
May not disturb sleep
Patients may not appear to be in pain
May be in odd distribution (e.g. a quadrant of the body; corner of mouth; ipsilateral mouth and hand – the cheiro-oral syndrome)
Onset may be delayed by weeks, months or years
Is usually persistent, but influenced by factors such as movement, emotion, temperature change

Table 22.3 Some clinical findings in central pain.

Pain is experienced within the area of the sensory deficit or a smaller area
The sensory deficit, if selective, is most typically thermal or for pain, and sometimes only detectable by quantitative sensory testing
There may be various spontaneous or evoked sensory phenomena (e.g. allodynia), typically seen with neuropathic pain
Rarely, central pain occurs in the absence of detectable sensory impairment; conversely, pain can occur in an anaesthetic area (anaesthesia dolorosa)
There may be variable accompanying motor and autonomic features

Multiple sclerosis

Whilst once thought uncommon and rarely mentioned in textbooks, pain in multiple sclerosis (MS) (see Chapter 10) is now known to be an important, common and often a major and dominating feature of the illness. Over 50% of patients with MS have chronic pain, and sometimes pain can be the presenting feature. Again, and similar to the pains seen in spinal cord injury, there are often a number of components. These range from nociceptive musculoskeletal pains due to factors such as spinal deformity, frozen shoulder, contractures and bedsores, to neuropathic pain from somatosensory damage in the spinal cord, brainstem and other cerebral structures. In contrast to spinal cord injury, the precise time of onset of the lesion is rarely known, and in view of the multiple lesions present, identification of the specific lesion responsible for the pain is rarely feasible. Both acute and chronic pain states may occur, as shown in Table 22.4.

Some further aspects of pain suffered by MS patients deserve comment:

- Surprisingly, the prevalence of pain in patients with MS is not significantly different to the prevalence of pain in the general population: pain is very common in the community. Pain intensity, the need for analgesics, and the impact on activities of daily living, however, are greater in patients with MS.

Table 22.4 Acute and chronic pain in multiple sclerosis.

Acute	Chronic
<1 month Trigeminal neuralgia Lhermitte's phenomenon Paroxysmal neuralgic burning extremity pain Optic neuritis Painful tonic spasms	>1 month Dysaesthetic lower extremity pain Back, joint and musculoskeletal leg pains Painful leg spasms Visceral pain
Treatment: often responds to carbamazepine or phenytoin	Treatment: those used for neuropathic pain (including, rarely, intrathecal drugs, e.g. baclofen); standard treatments for back pain when present; antispastic agents for leg spasms
Mechanisms: in paroxysmal symptoms, ?ephaptic transmission at site of demyelination	Mechanisms of central pain: uncertain – spinothalamic tract fibre loss +/– posterior column involvement probably implicated

- There is controversy as to whether pain in MS is associated with increasing duration of the illness and with age. In respect of depression or cognitive impairment, there does not appear to be any difference between patients who have pain and those who do not.
- Back pain often arises from muscle and joint structures.
- Trigeminal neuralgia may occur as an isolated phenomenon, or as part of the established disease. It is often due to a plaque in the region of the trigeminal nerve root entry zone. MS accounts for over 1% of patients with trigeminal neuralgia, and about 1–5% of patients with MS have trigeminal neuralgia. MS should be suspected in younger patients with trigeminal neuralgia, if the neuralgia is bilateral but not necessarily simultaneous, and if there are abnormal sensory signs. Drug treatment is the same as for the idiopathic condition, but surgical or other invasive intervention is only occasionally considered because of the commonly remitting course of MS.
- Optic neuritis is painful in 90% of patients. Pain, which rarely affects sleep and generally subsides in a few days, may result from the swollen optic nerve causing traction on the meninges.
- Brief paroxysmal pains, including tonic painful spasms, are typical but not diagnostic of MS. These usually respond to carbamazepine, often at low dosage.
- Lhermitte's phenomenon rarely needs treatment, but carbamazepine is an appropriate drug to consider.
- About one-third of patients with MS and pain have central pain, and the most distressing dysaesthetic pains are often accompanied by allodynia and other abnormal sensory phenomena. As with CPSP and spinal cord injury pain, impaired spino-thalamic function is often detected on examination. This impairment is probably necessary but not sufficient for pain to develop. There is also evidence that involvement of other tracts, in particular the posterior columns, may be implicated. Whilst experimental MRI of the cord in animals is beginning to be helpful in identifying pain-subserving pathways, precise clinical correlation between the painful symptoms and signs is rarely possible.

Table 22.5 Pain following spinal cord injury.

Musculoskeletal pains, including spinal pain from instability and deformity, shoulder disorders, muscle spasm, secondary overuse, and pressure syndromes
Segmental pain, sometimes with a band of hyperaesthesia, at the level of injury: central (from the spinal cord) +/– peripheral (from nerve roots, including cauda equina damage)
Spinal cord pain below the level of injury: central pain, sometimes with persistent dysaesthesias. Like central post-stroke pain, onset may be delayed months or years. Spinothalamic dysfunction is probably a necessary but not a sufficient factor. Particular conditions include the central cord syndrome and post-traumatic syringomyelia
Deep visceral pain, which may be a form of central pain. There may be associated autonomic dysreflexia
Phantom pain below the level of injury
?Complex regional pain syndrome

Spinal cord injury

Over two-thirds of patients with spinal cord injury have chronic pain and in one-third of them this is severe. Central pain can occur even when the cord lesion is complete, and after spinal cord surgical transection. Thus, severing the cord has no therapeutic benefit because rostral sequelae ensue: for example, abnormal spontaneous firing in dorsal horn neurones has been recorded immediately above a lesion at L1 in a paraplegic patient. Incomplete cord lesions and gun-shot injuries possibly more frequently cause pain than other cord injuries.

Pain following spinal cord injury often comprises an unusually large number of possible components, ranging from musculoskeletal nociceptive to neuropathic spinal cord pain (Table 22.5).

It is important to dissect out these various components, the mechanisms of which are different, in order to try and manage the pain appropriately. As usual, it may be easier to deal with the nociceptive (musculoskeletal) than the neuropathic pains. For example, attention to abnormal spinal posture, or management of a frozen shoulder, is more likely to be rewarding than dealing with central neuropathic pain.

The central pain associated with spinal cord trauma has similar characteristics to the pain associated with other lesions of the spinal cord, not only including MS, but also expanding or compressive lesions such as tumours and syringomyelia, and vascular damage. Management of pain from spinal cord lesions is the same as for other central pains and is discussed below. Surgery rarely has a part to play. The exceptions are pain due to post-traumatic syringomyelia, which rarely may respond to decompression; and pain at the level of injury which occasionally responds to dorsal root entry zone (DREZ) lesioning – whereby afferent impulses are interrupted as they enter the dorsal horn. DREZ lesioning has also been used to treat pain due to brachial plexus lesions, in which segmental central and peripheral pains may both occur. Spinal cord stimulation may be helpful in patients with partial lesions.

The central cord syndrome

An unusual syndrome is occasionally seen following sometimes even minor hyperextension or flexion injuries of the cervical cord. There is often weakness greater in the upper than lower limbs, and a striking feature is pain, with burning and stinging sensations and hyperpathia, affecting the chest and upper limbs. This pain is sometimes sufficiently severe that investigations are carried out to exclude upper limb fractures. The pain, which often resolves over some weeks, is probably due to damage to the spino-thalamic fibres at their decussation in the spinal cord.

Central spinal pain: some anatomical and pathological considerations

How spinal, and indeed cerebral, lesions affecting somatosensory pathways cause central pain is unclear. Most theories invoke either excitation of damaged sensory pathways, or diminution of inhibitory processes, or perhaps both. There are tracts in the dorsal and ventral segments of the spinal cord that mediate transmission of excitatory and inhibitory influences to and from the brain.

Pain transmission reaches the brain via two types of ascending spinal pathways:

- *The spino-parabrachial pathway:* this originates in Lamina I within the superficial dorsal horn and projects to the parabrachial region of the brainstem, peri-aqueductal grey matter and more rostral structures including hypothalamus and amygdala. The pathway is concerned with affect.
- *The classic spinothalamic pathway:* this ascends in the anterolateral quadrant of the spinal cord, terminates in the more posterolateral thalamus and projects to sensory cortex. It is implicated in discrimination and localization of pain.

Increasingly recognized as distinct entities, these ascending pathways mediate distinct sensory and affective components inherent in pain.

There are major descending pathways from the sensory cortex, thalamus, hypothalamus and brainstem to the spinal cord. Some of these pathways inhibit spinal nociceptive processes. Evidence in humans for central inhibition includes:

- Drugs with enhancing effects on noradrenaline and serotonin, neurotransmitters thought to inhibit pain and present in descending inhibitory pathways, may alleviate pain. Conversely, drugs and toxins such as reserpine, p-chlorophenylalanine and strychnine that block serotonin and GABA can produce pain.
- Stimulation of cerebral and spinal structures thought to be implicated in inhibitory processes can improve pain. This phenomenon is discussed below in the context of management of neuropathic pain.

Recently, the importance of descending excitatory pathways has been recognized, the key relay station being the rostroventromedial medulla, the output from which contributes to hyperalgesia. The evidence that excitation of the central nervous system can cause pain in humans includes:

- Pain can occur in an epileptic attack, including post-stroke epilepsy.
- Therapeutic stimulation of parts of the somato-sensory central nervous system can inadvertently cause pain.
- Abnormal neural activity coinciding with pain has been recorded – for example, in the thalamus, midbrain and spinal cord in some patients with on-going central pain.
- Anticonvulsants and local anaesthetics may alleviate central pain.

Apart from excitation and inhibition, numerous other factors, including effects resulting from cortical and thalamic plasticity and changes in affective processing of pain, are of major importance, and some of these factors are referred to elsewhere.

Pain and dementia

As cognition worsens, the reporting of pain by patients decreases. Pain in dementia presents a number of difficult issues:

- When communication and memory are impaired, assessing pain becomes problematic and often relies more on observation than on enquiry or use of a pain scoring system.
- Dementia tends to occur in older people, in whom co-existing degenerative joint and other often painful diseases become more frequent. Thus whether pain is due to a nociceptive cause, rather than a neuropathic component inherent in the dementing processes itself, may be difficult to determine.
- There tends to be under-treatment of pain in the elderly, or at least less consumption of analgesics, regardless of the presence of dementia, but particularly if dementia is present.

Patients with dementia have for long been known to have a reduced incidence of headache following lumbar puncture (2%, compared with up to 40% of non-demented patients). However, whether this finding necessarily results from the dementing process itself or from brain shrinkage is unclear. Compared with patients with Alzheimer's disease, those with frontotemporal dementia often show a loss of awareness and response to pain and can sustain injuries of which they appear unaware. This contrasts with the exaggerated response to sensory stimuli shown by some patients with semantic dementia (see Chapter 7). Also of note are patients with variant Creutzfeldt–Jakob disease (CJD) who may complain of pain in the limbs, trunk and face, and other sensory disturbances. MR imaging reveals characteristic hyperintensity of the posterior thalamus (pulvinar), a structure likely to be involved in pain processing.

There has been an increased understanding of the two systems thought to be implicated in the experience of pain. As discussed elsewhere, the medial pain system is thought to be important in the emotional and affective processing of pain, and the lateral pain system in the sensory and discriminatory pain processing. Furthermore, there is now compelling evidence that within the brain there are different circuits involved in the parallel processing of pain: the sensory components are predominantly processed in the somato-sensory cortex, and the affective and motivational components in the cingulate, insular and prefrontal cortex. In the later stages of frontotemporal dementia, in keeping with the impaired response to pain, limbic structures including the hyopothalamus and amygdala are involved. In patients with Alzheimer's disease the medial structures such as intralaminar thalamic nuclei tend to be affected, and consistent with this distribution is that these patients have unchanged or only a moderate reduction in thresholds for pain perception. However, their experience of pain is less intense, and experimentally they have impaired autonomic responses to acute pain stimuli.

Parkinson's disease and other movement disorders

The prevalence of pain in Parkinson's disease has been estimated to occur in 40–85% of patients. Apart from central neuropathic pain associated with the neurodegeneration, pains from osteoarthritis and other musculoskeletal causes are common, often severe and frequently overlooked, although they tend to be more amenable to treatment (see Chapter 5). In some patients these musculoskeletal pains are due to the degenerative changes associated with ageing. In others the Parkinson's disease itself contributes to their development. Pain in Parkinson's disease may be due to various factors (Table 22.6).

The presumed central pain of Parkinson's disease comprises a variety of types, including burning, stabbing, tingling, itching, tense feelings and restlessness. These symptoms can precede the onset of the motor symptoms sometimes by several years. Pain is often bilateral but can sometimes be more marked on one side, either ipsilateral or contralateral to the predominant motor features. Of interest because of its midline distribution, pain may involve the mouth, throat, or genital regions, suggesting in some instances a link with the burning mouth syndrome and vulvodynia (see below). The diurnal relationship between pain and any relief with levodopa or dopaminergic medication often seems unclear. Although levodopa has occasionally been used as an analgesic drug in other conditions, it is rare that pain experienced by a Parkinson's patient can be switched off simply by anti-parkinsonian drugs. Whilst pain due to stiffness may improve when the stiffness improves, any temporal relationship between dystonia, dopaminergic deficiency and drug administration needs to be evaluated on an individual basis, but is unpredictable. Pain due to focal dystonia, as might affect the hallux or produce a clenched fist, sometimes responds to botulinum toxin injections.

Table 22.6 Pain in Parkinson's disease.

Musculoskeletal factors: shoulder stiffness, spinal deformity including scoliosis and camptocormia (bent spine), arthritis, contractures
Limb rigidity and stiffness
Dystonia, dyskinesia, akathisia
Restless legs and sleep-related pains
Visceral pains: abdominal pain. This is sometimes (but not necessarily) related to constipation. Also: non-cardiac chest pain
Central neuropathic pain

The mechanisms of central pain in Parkinson's disease are poorly understood. Compared with controls, these patients have lower pain thresholds to heat, especially in their affected limbs, and regardless of whether the patients are 'on' or 'off'. This is the opposite to the raised thresholds sometimes seen in CPSP, suggesting there may be different mechanisms. Dopamine has analgesic properties and is present in descending spinal as well as ascending pathways. Furthermore, there are inhibitory pathways which project from the basal ganglia and brainstem to the spinal cord and which contain enkephalins, substance P, noradrenaline, serotonin and other neurotransmitters implicated in endogenous pain control. It is therefore not surprising if degeneration of these extrapyramidal pathways in the brain and spinal cord gives rise to central pain, and conversely that pallidal deep brain stimulation may improve pain. Mechanisms underlying the pain of the co-morbidities such as osteoarthritis, spinal deformity and muscle stiffness are of course entirely different.

Pain may also be associated with other extrapyramidal and related degenerative disorders. In pure autonomic failure (Chapter 23) and multi-system atrophy (Chapter 5), intense discomfort known as coat-hanger pain may occur. This pain around the shoulders and upper arms is likely to be due to ischaemia in suboccipital and paracervical muscles. The ischaemia is associated with increasing degrees of postural hypotension, and thus the pain occurs when the patient is upright, particularly in the mornings and after meals, and is relieved by lying flat. Amongst various often ill-defined sensory symptoms, pain may be an important feature of various dystonias and tics, in particular Tourette's syndrome and spasmodic torticollis – in which there is evidence of central pain in addition to pain related to musculoskeletal components. Other combinations of pain and involuntary movements are encountered in the syndrome of painful legs and moving toes, complex regional pain syndromes (CRPS), and stump and phantom phenomena.

Painful legs and moving toes syndrome

On the borderland between a central and peripheral neurological disorder and with movement-related and sensory components, the clinical features are summarized in the title: there is pain in the distal lower limbs accompanied by spontaneous movements of the toes, foot or sometimes lower leg. The pain varies from being a mild discomfort to a very severe intractable pain; rarely, instances of suicide have occurred. The pain is often difficult to describe and can be burning, crushing, cramping or twisting. The movements are rather slow and irregular with sinuous fanning and clawing of the toes. The number of toes affected is very variable. Sometimes the movements can be briefly stopped with effort, but then they break through again. In some patients pain precedes the onset of the movements; in others, it is vice versa. The condition may start unilaterally, although it tends to become bilateral, if sometimes asymmetrical. A similar phenomenon, 'painful arm and moving fingers', has also been described.

Often the cause is unknown, but lumbar root lesions associated with degenerative spine disease, peripheral neuropathy and peripheral limb trauma may be relevant factors. Rarely, other involuntary movements may be seen, which, as with the upper limb syndrome, suggests there may be a central rather than peripheral cause in some patients – a distinction that might possibly be clarified in future from neurophysiological studies.

Treatment is usually ineffective, for both the movements and the pain. For the pain, drugs including anticonvulsants such as gabapentin, antispasticity agents, benzodiazepines, phenothiazines, dopaminergic drugs and beta-blockers have not proven effective in the long term. Epidural opiates and local anaesthetics have been tried, and whilst initially lumbar sympathetic blockade was thought promising, this has not proved beneficial in most patients. The main disorder with which painful legs and moving toes is confused is the restless legs syndrome, although the distinction can usually be made with ease (Table 22.7).

Epilepsy

Pain may be a feature of an epileptic attack, as first noted by Gowers in 1901. Although rare, some studies have reported about 2% of patients with epilepsy have painful seizures, but this figure is probably an overestimate due to selection bias. The pains have been divided into three categories:

1 Unilateral pain in the face, arm, leg or trunk. Seizures tend to originate from the hemisphere contralateral to the pain, usually in the Rolandic area. Parietal, or occasionally centro-parietal or other lesions may be present, but sometimes no obvious structural lesion is detectable. Pain may be due to direct excitatory involvement of the primary sensory area or spread there from elsewhere. Ictal depression of inhibitory processes could be an alternative mechanism.

2 Headache. Distinct from the common post-ictal headache, headache and other head pains, sometimes with a migrainous element, may be part of the seizure. Temporal lobe involvement may be more common in these patients although localizing value is often poor. Increased cerebral blood flow occurs during a seizure, and it is thought that vascular factors may contribute to these pains.

3 Abdominal pain, rather than nausea, is a very rare feature of an epileptic attack and may be associated with temporal or frontal lobe seizures.

The treatment is that of the seizure disorder.

Peripheral nerve pain

Anatomical and pathological considerations

Pain from the periphery is conveyed to the central nervous system by primary afferent nociceptors: sensory neurones that are activated by noxious mechanical, thermal and chemical stimuli. These neurones contain thinly myelinated, faster conducting Aδ fibres and unmyelinated, slower conducting C fibres; the former mediate brief, acute, sharp first pain, and the latter the delayed, more diffuse, dull second pain. The majority of Aδ and C fibres are polymodal, i.e. they react to a variety of noxious stimuli, and these fibres use numerous signal-transduction mechanisms in order to convert noxious environmental stimuli into electrochemical signals. C fibres have been further tentatively subdivided into:

- Fibres that, amongst other properties, express P2X3 purine receptors (one type of ATP-responsive channel) and receptors for glial cell line-derived neurotrophic factor (GDNF). These fibres are sensitive to GDNF, terminate deep in the substantia gelatinosa of the spinal cord, and may be important in mediating neuropathic pain.
- Fibres that contain peptides including substance P and CGRP, and express the high affinity NGF receptor TrkA. These fibres are sensitive to NGF, terminate more superficially in the dorsal horn

Table 22.7 Painful legs and moving toes and restless legs syndromes.

Painful legs and moving toes	Restless legs syndrome
Spontaneous movements of toes and feet	Irresistible desire to move legs around
Present throughout day	Worse in evening and night, sometimes associated with periodic limb movements during sleep
No known family history	Often positive family history
Involuntary irregular, fanning, sinuous, dystonic movements affecting toes in particular	No spontaneous involuntary movements
Pain deep, diffuse, of various sorts	Pains of various sorts, also dysaesthesias, discomfort
Underlying causes sometimes seen, including peripheral neuropathy and radiculopathy, infections, and trauma; rarely, central causes	Underlying causes occasionally seen, including peripheral neuropathy and radiculopathy, iron deficiency anaemia, pregnancy, renal failure
Rarely responds to dopaminergic drugs	May respond to levodopa and dopaminergic drugs, benzodiazepines, opioids, anticonvulsants

of the spinal cord, and mediate plasma extravasation and vasodilatation – also called neurogenic inflammation. This inflammation, whether resulting from tissue damage or from release of peptides and neurotransmitters from the sensory nerve endings themselves, sensitizes nociceptor endings. This results in peripheral sensitization. These fibres are an important component of visceral afferents and have a more diffuse pattern of innervation compared with those fibres innervating skin. They also appear to regulate the behavioural sensitivity to pain through projections to deep central brain structures in the brainstem, hypothalamus and amygdala.

Both groups of C fibres respond to noxious stimulation and express the vanilloid (capsaicin) TRPV1 receptor which transduces noxious chemical and heat (>43°C) stimuli. Noxious cold (<15°C) is mediated by the menthol and a variety of other cold receptors. Chemicals such as bradykinin, serotonin, lipids and low pH stimulate other specific receptors. Mechanical stimuli are transduced by yet other receptors, less well characterized.

Some noxious stimuli affect ion channels and alter neuronal excitability directly; others involve metabotropic receptors and act through second-messenger processes. Several voltage-gated sodium, potassium and calcium ion channels are also expressed in sensory nerves, some specifically in C fibres, and a number of these are likely to be involved in transmission of nociceptive information. However, the selective properties of nociceptors change after damage or disease. For example, there are silent or sleeping nociceptors that acquire mechanical sensitivity only during inflammation.

There are many ways in which these peripheral phenomena and their central sequelae might generate pain. These include:

- *Ectopic discharges.* Discharges from damaged but also adjacent non-damaged neurones, the latter perhaps implicating Schwann cells, may generate various pain-producing substances. These ectopic discharges may not only generate spontaneous sensations, but also lead to changes in excitability of neurones in the central nervous system. The mechanisms responsible are likely to relate to changes in specific ion channels. Substances that block neuronal activity (e.g. local anaesthetics, mexiletine, some tricyclic antidepressants) which are sometimes effective for neuropathic pain may work through effects on specific ion channels.
- *Changes in neuronal properties.* Genes expressed in primary sensory nerves are eventually responsible for transduction, conduction and synaptic transmission. Disorders affecting the sensory nerve result in changes in up- and down-regulation of these genes and their transcripts, and changes in the function and selectivity of the nerves. For example, the $\alpha 2\delta$ calcium channel subunit is up-regulated after nerve injury, which may explain the efficacy of gabapentin in neuropathic pain (see below).
- *Loss of sensory neurones.* After peripheral damage, atrophy occurs which affects the whole of the sensory neurone. This loss particularly affects C fibres, and the resulting imbalance may contribute to abnormal sensations, as in some patients with post-herpetic neuralgia in whom areas of severe sensory loss may occur. The central ends of C fibres atrophy in the dorsal horn; whether adjacent Aβ fibre terminals sprout into that area remains controversial, but innocuous mechanical stimuli become perceived as pain (mechanical allodynia). This is an example of central sensitization, a phenomenon shown, for example, by some patients with post-herpetic neuralgia.
- Central sensitization after lesions of peripheral sensory nerves occurs not only in the spinal cord but also at higher levels. Central sensitization is associated with various features: enlargement of the area in the periphery where stimuli activate neurones; subthreshold stimuli now reach threshold; increased response to suprathreshold stimuli; and pain from activity in non-nociceptive fibres. Some of these phenomena account for pain that spreads beyond the affected nerve territory, exaggeration and prolonged pain after peripheral stimulation, and other features including allodynia, hyperpathia and related sensory disturbances (see below).
- Contrasting with these excitatory processes, disinhibition may also be important. Normally GABA and glycine mediate inhibition of pain-subserving processes. Blocking these substances can cause pain. Nerve injury may result in impaired GABA inhibition in the spinal cord.
- Microglia and other glial cells are intimately involved in the neuro-immune responses that follow neurological lesions of the central nervous system and which can generate pain. There are also peripheral immune responses that may be associated with peripheral nerve damage and a number of painful peripheral nerve disorders.

Painful peripheral neuropathies

It is puzzling why some patients with a specific neuropathy develop pain, whereas others do not. Furthermore, pain in some neuropathies may be due to several different aetiologies. For example, in diabetic neuropathy there are vascular, inflammatory and metabolic factors. In HIV neuropathy, there are direct effects of the virus, nutritional factors, vasculitis, toxicity from antiretroviral agents, and co-infection. Painful neuropathies, a few examples of which are singled out below, can be roughly classified into causative groups:

- Inflammatory and vascular disorders – diabetes, collagen vascular disease and vasculitis, Guillain–Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Many of these disorders cause mononeuritis multiplex, and to what extent vasa nervorum and nervi vasorum and sympathetic nerve fibres are implicated is uncertain. Changes in the neurochemical milieu surrounding damaged nerve endings, some of which may follow leakage from damaged blood vessels, may well be important.
- Infective – Lyme disease, HIV, leprosy.
- Infiltration of nerves – sarcoid and tumours.
- Metabolic factors – diabetes, alcohol, nutritional and vitamin deficiency states (especially thiamine and vitamin B_{12} deficiency), peripheral ischaemia and paraneoplastic states.
- Toxic and drug-induced causes:
  - chemotherapeutic agents (e.g. vincristine, cisplatin, taxol), antiretroviral drugs, nitrofurantoin, gold, isoniazid, disulfiram;
  - toxic agents – arsenic, thallium.

- Trauma, including iatrogenic lesions after surgery.
- Hereditary peripheral neuropathies (and see Absence of pain, below).

Burning feet, and the small-diameter fibre neuropathies

Although autonomic and later large fibre involvement may occur, burning pain, typically distal and affecting the feet, is often due to a small fibre sensory neuropathy. Whilst nerve conduction is typically normal, there may be abnormalities of thermal thresholds. However, not only is the latter a psychophysical test requiring patient co-operation, but abnormalities do not prove that the neuropathy and hence the pain arise peripherally. Sometimes a small fibre neuropathy is only detectable on skin biopsy. It is striking how many of the painful neuropathies are accompanied by autonomic involvement, presumably because small-diameter fibres are those subserving both efferent autonomic and afferent sensory modalities. Causes of these small-fibre neuropathies include:

- Diabetes, which deserves particular mention because this may only be revealed by a glucose tolerance test. Thus, in an otherwise obscure case of peripheral neuropathy with burning pain, diabetes needs to be carefully excluded.
- Connective tissue diseases such as Sjögren's disease and monoclonal gammopathy.
- Acquired amyloid.
- Genetic causes (see below), which perhaps account for an otherwise cryptogenic burning feet syndrome more frequently than usually suspected.

As with so many other painful conditions, non-neurological causes need to borne in mind, and with pain in the feet, even when burning, disorders such as plantar fasciitis are an occasional trap for the unwary.

Erythromelalgia

First recognized and named in 1872 by Weir Mitchell, the physician during the American Civil War who wrote *Injuries of Nerves and Their Consequences*, this term comprises a group of poorly defined symptoms that appear to have variable combinations of vascular and neuropathic features. The characteristic features include episodes of heat, redness and pain in the extremities, predominantly the legs, worse and prolonged in the heat, and with improvement in the cold such that, for relief, patients sometimes immerse their feet in cold water to an extent that skin maceration and other complications develop. The episodic features and heat triggering differentiate erythromelalgia from small fibre neuropathies, CRPS, and vascular insufficiency. Erythromelalgia can be divided into:

- Primary:
  - sporadic;
  - hereditary (childhood onset, autosomal dominant).
- Secondary, to thrombocythaemia and less commonly polycythaemia, collagen vascular disease, diabetes, peripheral neuropathy, drugs (e.g. calcium-channel blockers, pergolide, bromocriptine), following cold injury, and rare toxic causes.

Whether the clinical features are due to vascular factors, a small fibre neuropathy or a combination, the various components may have a final common pathway in which there are abnormalities of microvascular perfusion of the skin, with a combination of skin hyper-perfusion together with hypoxia.

Neurological investigations have variously shown evidence of abnormalities in both afferent C fibres and efferent post-ganglionic sympathetic fibres in a number of patients, but the precise relationship between such abnormalities and the vasomotor changes remains unclear. There is evidence suggesting that, by different mechanisms depending on the cause, there is sensitization of polymodal C nociceptors, with abnormally low thresholds and prolonged after-discharges, and involvement of mechano-insensitive fibres. The axon reflex results in vascular leakage and vasodilatation. The hereditary form probably results from mutations in the *SCN9A* gene encoding the Na(v)1.7 voltage-gated sodium channel. Recently, the very rare paroxysmal extreme pain disorder (familial rectal pain syndrome) has been shown to be a channelopathy due to a disorder affecting the same gene. How any of these mechanisms give rise to the episodic nature of the clinical features remains unanswered.

Treatment

- Remove offending drug: condition often resolves.
- Low-dose aspirin when due to thrombocythaemia: often effective.
- Epidural analgesics and other symptomatic measures: rarely effective.
- High dose topical capsaicin to damage C fibres: experimental and unlicensed.
- Avoid damage from cold immersion.

Diabetes

Pain occurs in over 10% of patients with Type I and one-third of patients with Type II diabetic peripheral neuropathy, but what characterizes those patients with pain is unknown, even when their nerves are studied by microneurography. The classification shown in Table 22.8 is both arbitrary and a simplification, but illustrates the variety of types of painful neuropathies encountered. Individual patients often have more than one type of nerve involvement. In painful neuropathies of acute onset, vascular and inflammatory factors may be particularly important and pain is more likely to be reversible; by comparison, metabolic factors probably predominate in those neuropathies of gradual onset, in which pain may be persistent.

Some of these diabetic neuropathies merit particular mention:

- Acute painful neuropathy, associated with rapid weight loss, has a good prognosis over months. 'Insulin neuropathy', i.e. a neuropathy that develops as insulin is introduced, again has a good prognosis. Both conditions are uncommon.
- About 50% of diabetic third cranial nerve palsies are painful. Pain presumably arises from involvement of associated trigeminal afferents and resolves over days or a few weeks.

Table 22.8 Varieties of painful diabetic neuropathy.

	Acute onset	Chronic onset
Symmetrical	Acute distal sensory neuropathy 'Insulin neuropathy'	Peripheral polyneuropathy, particularly with small-fibre involvement Associated with CIDP
Focal and multifocal	Cranial neuropathy – IIIrd nerve palsy Truncal neuropathy Lumbosacral radiculoplexopathy Isolated (compression) peripheral neuropathy	Lumbosacral radiculoplexopathy Isolated (compression) peripheral neuropathy Associated with asymmetric CIDP

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy.

- Truncal involvement can mimic acute cardiac or abdominal disorders, and shingles without a rash. Pain resolves over months.
- Lumbosacral radiculoplexopathy (diabetic amyotrophy; femoral neuropathy) is typically seen in late-onset diabetes in older men. There is severe aching thigh pain, worse at night. Gradual resolution occurs over months. The differential diagnosis includes lumbar root compression, pelvic malignancy, CIDP and vasculitis. A similarly painful plexopathy affecting the upper limb has been described.
- The most common and most intractable painful neuropathy is a distal polyneuropathy, worse at night or with stress. Most information on treatment is derived from studies on this group of patients, in whom pain has a severe and long-lasting impact.
- The painful diabetic foot can be due to neuropathic or neuro-ischaemic factors. Infection, including osteomyelitis, may need to be excluded, and meticulous foot care is essential.

Treatment, usually with drugs, is as for any other painful peripheral neuropathy (see below). Optimal control of blood sugar should always be attempted, but glycaemic control in late-onset diabetes does not appear to be a predictor of painful neuropathy.

Guillain–Barré syndrome

Pain commonly affects patients with this condition and can sometimes be the first symptom, and a particularly prominent one. Pain affects mainly the low back, buttocks and backs of the thighs and is muscular in character – reminiscent of the pain seen in poliomyelitis, as well as in some of the inflammatory myopathies. The pain is often under-recognized and can be particularly difficult to manage in a patient who may be at the same time paralysed and cognitively intact. Opiates, particularly in the early stages, may be required.

Neuralgic amyotrophy (brachial neuritis)

This condition (see also Chapter 9) is almost, but not always, extremely painful. Characteristically the patient experiences acute pain around the shoulder girdle, followed days or a few weeks later by weakness, often producing winging of the scapula, and there may be patchy areas of sensory loss. There is histological evidence for sensory as well as motor nerve involvement. The characteristics of the pain are its severity, its diffuse and nagging quality, and sometimes the worsening with limb movement. The author has found that the pain almost invariably seriously affects sleep. The pain will usually subside over some days or weeks and strong analgesics may be required in the initial stages, but there is no specific treatment available. Steroids are unhelpful.

Painful inherited neuropathies

The inherited neuropathies (see Chapter 9) associated with pain are rare. However, they have a particular importance because in some the underlying mechanisms are beginning to be clarified. Examples of these neuropathies include:

- Hereditary sensory and autonomic neuropathy (HSAN) Type I. In most families there are *SPTLC1* gene mutations, and patients present with sensory symptoms including lightning pains during their teens or young adult life.
- Fabry's disease. The paroxysmal painful symptoms, which date back to childhood, bear some resemblance to erythromelalgia (see above). How the abnormal sphingomyelin accumulation in the nerves, and any vascular component, generate the pains is unclear. Pain may be improved after prolonged treatment with agalsidase alfa – a form of enzyme replacement therapy.
- Familial amyloid neuropathies.
- Tangier disease.
- Primary erythromelalgia (see above).

Iatrogenic painful peripheral nerve lesions

In contrast to the expected pain that often follows accidental injury to a peripheral nerve, painful peripheral nerve lesions following surgery are often under-recognized. For example, post-surgical neuralgia persisting after 1 year has been reported in 41–61% of patients after thoracotomy, 27% of patients after mastectomy, and 28% of patients after saphenous vein surgery. Intriguingly, pain after Caesarian section almost never occurs. Whilst management follows along conventional lines, in certain instances nerve repair can achieve satisfactory resolution of pain. A striking example is repair of the spinal accessory nerve, occasionally damaged during lymph node exploration in the posterior triangle of the neck. This example is also of interest in that it signifies there must be an afferent component in a nerve considered to be solely motor.

Pain associated with benign orthopaedic conditions

Glomus tumour

These uncommon benign tumours, entirely unrelated to glomus jugulare tumours in the neck, are really hamartomas of the normal glomus body. The glomus body is an innervated arteriovenous anastomatic structure which may have a temperature regulating function. The afferent arterioles are tortuous, associated with glomus (endothelial) cells, and innervated by myelinated and unmyelinated fibres. Some 50% of glomus tumours affect the hand, often subungually, where they may appear as a little blue nodule. Such an appearance is not diagnostic of a glomus tumour, the differential diagnosis including melanomas, neuromas and neurofibromas. Glomus tumours can occur anywhere over the body, including within bone, but they are usually subcutaneous. The key clinical triad comprises:

- Severe and continuous pain;
- Extreme cold sensitivity (for instance, worsening pain by immersing the hand in cold water);
- Extreme tenderness (for instance, even the slightest contact of the nodule with the end of an orange stick induces quite exquisite pain).

Diagnosis is often straightforward when tumours are visible, but otherwise can be difficult. Plain radiographs may reveal bony erosion; otherwise detection may require ultrasound, MRI or angiography. Surgical removal is usually immediately curative.

Osteoid osteoma

This bony disorder occasionally presents to the neurologist as a cause of unexplained pain, usually in a limb. The cardinal features are the often severe and sometimes localized pain and characteristically extremely good response to anti-inflammatory drugs. The good response only lasts for the duration of action of these drugs. The reason for this responsiveness is that the fine nerve terminals in this benign tumour of bone are exposed to prostaglandins present in the tumour. The abnormal bony tissue may show as a focal radiolucent or sometimes radio-opaque nidus, often with surrounding cortical thickening. On isotope bone scanning this tumour produces a dramatic focal hot spot. CT scanning may also be useful. Gratifyingly, excision of the tumour is curative and immediate pain relief occurs.

Motor neurone disease

Although not typically classified within neuropathies, pain has been reported in 64% of 42 patients with motor neurone disease (MND) and in 57% of 124 patients admitted to a hospice. Pain is variously described as aching, cramping, burning, shock-like, or is indescribable. In some MND patients pain can be a dominant symptom, especially when weakness is not advanced.

The cause of this pain is ill-understood, although musculoskeletal factors and skin pressure (only rarely with pressure sores) are likely to operate. Central mechanisms may also be important. Just as with Parkinson's disease, pain may be one of the subjective sensory symptoms that can occur even long before serious disability develops, and in occasional patients with MND there is objective evidence of sensory involvement both clinically and on investigation. In many MND patients it is likely that the pain is due to a combination of musculoskeletal and neuropathic components, which may be partially or completely alleviated by medication, in particular opiates, especially in the later stages of the disease.

Painful peripheral viscero-somatic disorders

There are certain disorders sometimes referred to a neurologist that appear to involve the interface between cutaneous and visceral innervations. These neuropathic disorders include the burning mouth syndrome and vulvodynia.

The burning mouth syndrome

Contrasting with the severe, usually unilateral, paroxysmal stabbing pains of glossopharyngeal neuralgia, sometimes accompanied by syncope, the burning mouth syndrome embraces various types of persistent and unpleasant sensations within the mouth and includes terms such as glossodynia. Women are affected more than men, the mean age being 50–60 years. The clinical features comprise a burning sensation that is usually diffuse and bilateral, and any area within the mouth may be affected including the tongue. The pain is usually constant but can fluctuate in severity during the day. Influencing factors in some patients include eating (making symptoms either better or worse), stress, and previous dental procedures. There may be associated dryness of the mouth and loss or altered taste appreciation. The condition is usually long-lasting, although spontaneous improvement or recovery has been reported. Treatment remains empirical and includes drugs used for neuropathic pain, and cognitive–behavioural and other psychological therapies that may also be helpful for the depression and other psychological disturbances that often co-exist.

Although routine oral and sensory examination is normal, quantitative sensory testing suggests abnormality of small fibre function. There is also a reduction of epithelial nerve fibres, suggesting a trigeminal small fibre neuropathy. In some patients abnormalities of the blink reflex suggest more central involvement affecting the trigeminal system. Thus, at present the burning mouth syndrome appears to be a neuropathic disorder of unknown but probably various causes. These may involve both peripheral and central components, and there is some suggestion of nigro-striatal system involvement in the latter.

Vulvodynia

Different from many causes of perineal pain, vulvodynia comprises vulval pain associated with painful burning sensations, mechanical allodynia and hyperalgesia. Sometimes there is no spontaneous pain, allodynia only being provoked by touch and pressure. The disorder is likely to be multi-factorial and either primary or secondary to vulval or vaginal inflammatory or infective causes. Whilst surgical excision of the affected tissue has sometimes been advocated, conservative treatment with topical local anaesthetic cream, or oral amitriptyline, gabapentin or pregabalin is generally more appropriate.

The syndrome is probably another example of a neuropathic pain disorder, in turn related to reduced sensory thresholds to a variety of sensory stimuli. These abnormalities are likely to result from factors including increased innervation secondary to nerve sprouting or neural hyperplasia, and sensitization of thermoreceptors and nociceptors within the vaginal mucosa. The increased innervation in vulvodynia tissues is associated with increased expression of TRPV1 (vanilloid or capsaicin) receptors, a finding that might account for both the sensory disturbances and mild erythema sometimes seen. Some of the clinical and pathological features also occur in interstitial cystitis and related conditions.

Visceral pain

Visceral pain, mainly transmitted to the central nervous system through afferents running within sympathetic nerves, has characteristic features (Table 22.9).

These features, clearly different from those encountered in typical somatic pain, may be explained by various factors, including:

- Different molecular mechanisms that selectively transduce the various different peripheral chemical and mechanical stimuli, including ischaemia or distension, all which affect viscera.
- The contribution of processes that sensitize visceral afferents.
- The important contribution of silent afferents, which only become active in the presence of inflammation.
- Viscero-somatic convergence in the spinal cord, thalamus and cortex.
- Central spinal processes that result in amplification and persistence of afferent impulses from the damaged viscera.
- Ascending transmission of pain, via dorsal column and other non-spinothalamic pathways in the spinal cord, to specific brainstem nuclei, amygdala and hypothalamus – regions implicated more in affective than discriminative aspects of pain.

Visceral pain due to acute painful cardiac, gastrointestinal or urogenital disorders rarely presents to the neurologist. However, other aspects of visceral pain may have important practical aspects. Examples include odd distributions of pain (e.g. ear pain due to carcinoma of the lung), involvement of the viscera in shingles and perhaps post-herpetic neuralgia, and possibly various chronic painful conditions such as the irritable bowel syndrome, non-ischaemic cardiac pain, fibromyalgia and chronic pelvic pain. Some patients have a number of these latter disorders at the same or different times. Particularly in these individuals, underlying mechanisms may include abnormal sensitization of peripheral or spinal neurones or aberrant central processing of visceral sensation – so that stimuli usually innocuous to other people are perceived as painful.

Table 22.9 Characteristics of visceral pain.

Only evoked from some viscera (e.g. not from the liver)
Not always linked to injury
Diffuse and poorly localized
Referred to other sites
Accompanied by motor and autonomic responses

Plexopathies

The dorsal root ganglia and proximal roots of peripheral sensory nerves may be affected by conditions that result in pain, and, depending on their location, sometimes affect the spinal cord as well. Causes commonly presenting to the neurologist include infection (e.g. shingles and post-herpetic neuralgia), inflammation (e.g. arachnoiditis) and compression (e.g. tumours and discs). However, more peripherally, it is painful plexus lesions that sometimes prove particularly difficult to diagnose and manage. Amongst the various painful conditions, including the thoracic outlet syndrome affecting the upper limb, the three most serious disorders resulting in painful plexopathies are:

1. Trauma;
2. Malignancy;
3. Following irradiation.

Traumatic brachial plexus lesions

The most common cause is a traction injury, most typically following a motor cycle accident, in which there has been stretching or avulsion of the brachial plexus and sometimes the extradural and intradural nerve roots. Paradoxically, the introduction of crash helmets has made these injuries more frequent, because without head protection the patient was more likely to be killed. Traumatic plexus lesions are also frequently seen during warfare and usually result from missile injuries. Of interest from the developmental viewpoint is that lesions sustained in infancy are rarely painful.

Pain following trauma often develops immediately, but can develop or can increase in severity in the months following the initial trauma. The pain affects the limb in the distribution of the affected roots or plexus but is sometimes more widespread. It is often burning and very severe, dominating the patient's life. Despite attempts at treatment, the prognosis for improvement in the pain is very poor. Pain can persist indefinitely. Recently, studies of nerve repair following brachial plexus injuries have shown there is a correlation and temporal association between a reduction in de-afferentation pain and return of motor function, with the former preceding the latter. Such surgery, itself requiring exceptional surgical skills, has led to much interest in processes underlying recovery and pain relief, including the contribution of NGF and other growth factors.

Malignant and radiation-induced plexopathies

Metastatic disease or a primary tumour can infiltrate the cervical, but more commonly the brachial or lumbosacral plexus, causing severe and unremitting pain. Particularly if at the outset there are few or no neurological signs pointing to neural involvement, discovering the cause of the pain may be very difficult. Nevertheless, pain is often the presenting symptom, for example occurring in 75% of patients with brachial plexopathy due to cancer. It is due to malignant infiltration of the nerves themselves or of surrounding blood vessels and connective tissue. Involvement of adjacent structures such as bone may also cause pain. On other occasions pain will develop in a patient known to have, or have had, malignant disease, in which case a malignant cause will be suspected early.

Usually plexus involvement will become obvious when there are motor and sensory signs. When the lower trunk of the brachial plexus is involved, and Horner's syndrome accompanies the pain, a relatively proximal cause around T1 should be suspected, since it signifies involvement of the sympathetic trunk or ganglia (Pancoast's syndrome). Generally, pain is a major feature of malignant plexopathies; the absence of pain should lead to review of the diagnosis. Imaging will be the first step in evaluation.

Treatment of the pain will generally be managed by the oncologist or palliative care physician. This is because treatment is largely symptomatic and palliative, sometimes with radiotherapy, and a multi-disciplinary approach is required.

A particularly challenging problem is to decide whether, in a patient with known malignant disease and who has had radiotherapy, pain is due to the radiotherapy or to tumour recurrence. The distinction between malignant and radiation plexopathies is often very difficult. Some features that may be helpful, although not diagnostic, are shown in Table 22.10.

Frequently, neither the clinical features, nor the results of imaging studies, allow a definite distinction to be made in an individual patient who has previously received radiotherapy. Treatment of pain from radiation-induced plexopathies is unfortunately extremely limited and the outlook for pain relief is poor.

Shingles and post-herpetic neuralgia

Shingles

Shingles occurs when there is reactivation of the varicella-zoster virus (VZV), the smallest of the DNA-containing herpes viruses, that has remained latent in a trigeminal or dorsal root ganglion following an earlier acute infection. Reactivation is more likely when there is reduced cellular immunity as occurs with increasing age, immunosuppressive disorders and treatments, and in those with certain HLA tissue types; reactivation seems to occur less frequently in black people. In immunocompetent patients it is very rare that shingles signals an underlying malignancy or other predisposing factor. Investigation for an underlying cause is rarely necessary in isolated shingles.

VZV, which is both epithelial and neurotrophic, causes a painful segmental neuropathy with skin changes that typically include small blisters from which the virus can be isolated. Although the clinical diagnosis of shingles is nearly always straightforward from its appearance, rarely blisters with local pain and sensory disturbances are due to herpes simplex rather than zoster infections. Definitive distinction is possible from viral identification in the blister fluid. Rarely, shingles can occur in the absence of a rash (herpes *sine* zoster). However, without viral confirmation during the initial stages, shingles remains a clinical diagnosis – suspected when there is segmental pain associated with concomitant sensory changes. Both herpes simplex, and less commonly herpes zoster (in about 6% of cases), can recur. VZV is found in both small and large fibre sensory cell bodies in the dorsal root and trigeminal ganglia, i.e. it is not confined to nociceptive fibres, and it may cause pain through involvement of spinal NMDA receptors and possibly other mechanisms.

The pain of acute shingles can be of almost any sort and range from the trivial to the excruciating. Treatment during the acute stage is symptomatic with analgesics, and sometimes strong opiates may be required. Other practical questions may then arise in respect of the pain:

Table 22.10 Pain due to malignant plexopathy and radiation-induced plexopathy. From Jaeckle (2004) with permission.

	Neoplastic	Radiation
Presentation	**Pain**	**Paraesthesias, weakness**
Pain	Early, severe	Later in course
Plexus involvement		
Brachial	Often lower plexus	Usually whole plexus
Lumbosacral	Lower, usually unilateral	Commonly bilateral
Horner's syndrome (brachial plexopathy)	Common	Unusual
Local tissue necrosis	Not present	Common
Rectal mass (lumbosacral plexopathy)	Common	Absent
Myokymia	Unusual	Present
Nerve enhancement (MRI)	Present	Usually absent
PET scan	Positive	Usually absent

MRI, magnetic resonance imaging; PET, positron emission tomography.

- What predicts the development of post-herpetic neuralgia? The incidence of post-herpetic neuralgia increases with increasing patient age; a rule of thumb is that the percentage affected is that of the age. Fifty per cent of patients aged 50 will develop this complication and 90% at age 90. This prediction is now considered a pessimistic over-estimate, but nevertheless old age is undoubtedly the most important factor. In addition, female sex, the presence of virus in peripheral blood, severity of rash, severity of the acute shingles pain, prodromal pain and possibly a specific HLA haplotype are also thought to be risk factors. Reducing the viral load with antiviral agents is the rationale for their use during the acute phase to diminish the likelihood of post-herpetic neuralgia.
- Are antiviral drugs always indicated? These should be given if there is ocular involvement – when urgent referral for ophthalmic assessment is essential, and in the immuno-compromised. Whilst there is little firm evidence, meta-analyses suggest that there may be less prolonged pain and possibly a reduction in the incidence of post-herpetic neuralgia following early use of antiviral drugs, including aciclovir, valaciclovir and famciclovir. Compared to aciclovir the latter two drugs have better bioavailability with oral administration and also have the advantage of being taken three rather than five times daily. There are ongoing studies with brivudin, which can be given once daily, but it is not currently licensed in the UK. Brivudin is contraindicated when used with 5-fluorouracil.
- Are there other measures that will prevent the development of post-herpetic neuralgia? Steroids are ineffective. There is only one small study suggesting that early treatment with amitriptyline reduces the occurrence of post-herpetic neuralgia; large, appropriately controlled trials are needed. Furthermore, it is inevitably difficult to decide whether to recommend prophylactic drugs to prevent an uncertain but sometimes severe complication that might never occur, particularly in an elderly patient in whom drug-induced side effects are common. Neither sympathetic blockade nor a single injection of steroids with local anaesthetic is beneficial, and although prolonged somatic nerve blocks using an epidural catheter have been reported as being helpful, these are rarely a realistic prophylactic approach. Recent, impressive evidence suggests that a live attenuated vaccine reduces the incidence and morbidity of herpes zoster and also the incidence of post-herpetic neuralgia. The role of this vaccine as a preventative public health measure to protect a population as a whole remains to be clarified.

Post-herpetic neuralgia

Defining the time when pain from acute shingles becomes the chronic pain of post-herpetic neuralgia remains arbitrary. The most generally applied point is 3 months after the rash. Again, pain and other sensory disturbances range from the trivial to the most severe. Severe post-herpetic neuralgia is a common referral for pain management.

Post-herpetic neuralgia can comprise any form or multiple forms of pain, on-going or evoked, with or without itch. This heterogeneity may relate to the different ways in which the virus damages nerves, the underlying pain-related processes being subserved by combinations of sensitization and de-afferentation that give rise to various forms of sensory disturbance including sensory loss. Skin biopsies suggest that patients with neuralgia have fewer cutaneous nerve endings compared with pain-free patients, but in addition a variety of neurochemical changes occur in the affected skin. The spinal cord is also affected. Focal atrophy of the dorsal horn may occur, together with surprisingly long-lasting chronic inflammatory changes which have been detected even 2 years after the shingles.

Acknowledging the numerous mechanisms that mediate the different forms of pain, treatment nevertheless remains as empirical as it is for most other similar pains. Systematic studies provide evidence of benefit for tricyclic antidepressants, gabapentin and pregabalin, and opioids including morphine, oxycodone and tramadol. Topical treatments providing variable benefit include lidocaine patches, now licensed in the UK; aspirin in ether, benzydamine and capsaicin have also been used. Whilst capsaicin is licensed, it produces a burning sensation and is often poorly tolerated; great care is needed to avoid contact with the eyes. Just as in the management of epilepsy, there is no reason why combinations of drugs should not be tried, e.g. nortriptyline and gabapentin, especially when their modes of action are different and lower doses of each can be used.

Despite reports of numerous other treatments, ranging from transcutaneous electrical nerve stimulation to invasive procedures, the long-term benefit of these other techniques has not yet been established. One of the most recent claims has been for pain relief from intrathecal methylprednisolone, which reportedly provides excellent pain relief over follow up of 2 years, without reported complications. More extensive studies confirming these remarkable results are awaited.

Complex regional pain syndrome (CRPS) – reflex sympathetic dystrophy (RSD) and causalgia

No topic within the study of pain is as confused and confusing as the disorders that are subsumed by these and other related terms. Reasons for these difficulties include:

- The definition of the various disorders, and even their terminology, remain matters of debate and constant revision.
- Whether these disorders are due to a primarily neuropathic disturbance, or to an abnormal peripheral pseudo-inflammatory response, or a combination, is unclear.
- The contribution, if any, of the sympathetic nervous system is controversial. If it is involved, in what way is unclear, and clinical considerations are difficult to reconcile with experimental findings.
- Rather than there simply being a spectrum of components, many different disorders are probably subsumed under the various umbrella terms employed.
- Patients who have not been adequately diagnosed, or in whom a precise diagnosis cannot be established, often receive one of these or a related label – hence the frivolous view that RSD and

such disorders simply refer to 'a funny pain in a funny-looking limb'.

Although subject to ongoing revisions, IASP at present classifies CRPS into two forms. The definitions are shown in Table 22.11.

CRPS Type II is easy to identify since, by definition, there is a major nerve injury, although the term major has never been defined – thus, it would be debatable how to classify CRPS that might follow carpal tunnel decompression. CRPS Type II is most commonly seen during wartime, when bullet or other penetrating or crush injuries are frequent. Usually the pain comes on very soon after injury, although in 5% of patients pain develops after a few weeks. Median and sciatic nerve and plexus lesions are most commonly implicated, particularly when the lesions are incomplete. The pain is typically burning. It is usually continuous but can fluctuate, and there are often sensory disturbances including allodynia, hyperalgesia and hyperpathia. The pain is usually extremely severe, poorly localized, and typically distal, but there may be more diffuse spread up the limb. Contralateral pain may occur. Stress of any sort tends to worsen the pain, and classic accounts depict desperate soldiers in terrible pain that commonly persists indefinitely. The same pain can occur in non-combat situations, such as brachial plexus traction injuries, stab wounds and iatrogenic nerve injuries.

CRPS Type I has similar but often milder features than Type II and is far more common. Pain of Type I is usually in a distal extremity, often burning, both spontaneous and stimulus-evoked, worse with dependent posture and disproportionate to the initiating insult. There are numerous causes, the most common being trauma in perhaps 50% of cases. However, since trauma is so common, the incidence of CRPS Type I following trauma is very low, probably less than 1%. The trauma can be relatively minor, as in an upper limb sprain or after Colles' fracture, and can also follow minor surgery, e.g. for Dupuytren's contracture. Other causes are included in Table 22.12.

A similar syndrome can be seen in the lower limb. Sometimes particular forms of the syndrome are seen, for instance the shoulder–hand syndrome after myocardial infarction or lung disease. Transient and flitting forms of CRPS Type I are recognized, particularly in children and in pregnancy.

One of the major aspects of CRPS, whatever its cause, is the astonishingly wide range of features that may accompany the pain (Table 22.13). This again suggests CRPS embraces a variety of different conditions. Furthermore, many of the features can follow immobility and disuse, which can themselves cause a variety of central pathophysiological changes.

Whether certain patients are more likely than others to develop CRPS is much debated. Patients with CRPS probably do not have a predisposing psychiatric disease profile different from the general population. The contribution of psychogenic factors,

Table 22.11 Complex regional pain syndromes (CRPS): 1994 International Association for the Study of Pain (IASP) classification.

CRPS Type I (reflex sympathetic dystrophy [RSD]; algodystrophy; Sudeck's atrophy; minor causalgia)
A syndrome that develops after an initiating noxious event, is not limited to the distribution of a single peripheral nerve, and is apparently disproportionate to the inciting event. It is associated at some point with evidence of oedema, changes in skin blood flow, abnormal sudomotor activity in the region of the pain, or allodynia or hyperalgesia
CRPS Type II (causalgia)
Burning pain, allodynia, and hyperpathia usually in the hand or foot after partial injury of a nerve or one of its major branches

Table 22.12 Non-traumatic causes of complex regional pain syndrome (CRPS) Type I.

Disorders of the peripheral nervous system, e.g. herpes zoster
Disorders of the central nervous system, e.g. stroke, multiple sclerosis, spinal trauma, cerebral tumour, brain injury
Immobilization
Systemic illness, e.g. after myocardial infarct and cardiac surgery, lung disease
Pregnancy
Electric shock
Drugs, e.g. phenobarbital, isoniazid
Idiopathic

Table 22.13 Various clinical features seen in complex regional pain syndromes (CRPS). After Schott (1999) with permission from Oxford University Press.

Skin erythematous, cyanosed, pale or blotchy
Swelling or atrophy of skin
Excess or loss of hair
Nails ridged, curved, thin, brittle or clubbed
Dupuytren's and other contractures
Muscle wasting and weakness
Involuntary movements – tremor, dystonia, spasms
A syndrome comprising 'neglect' and other similar disturbances
Hyperacusis
Excessive, reduced or absent sweating
Inappropriate warmth or coldness
Loss of skin wrinkles or glossiness
Subcutaneous atrophy or thickening
Joint stiffness, acute or chronic arthritis
Osteoporosis – spotty, localized or widespread
Detrusor and urinary dysfunction
Hemi-sensory impairment outside the painful area
Alterations in visuospatial perception

particularly in relation to post-traumatic fixed dystonia and CRPS, and the contribution of genetic factors, remain unclear.

Currently it appears that in some patients, especially in the earlier stages of CRPS Type I, there is a pseudo-inflammatory state that accounts for the warmth, reddening, swelling and limitation of movement. The contribution of neurogenic inflammation is receiving increasing attention. Also important may be central inhibition of the regional sympathetic outflow to the limb, and, in those who spontaneously recover, there seems to be an evolution – the segmental sympathetic paralysis waning as the clinical features improve over some months. Contrary to what was previously thought, the autonomic nervous system is certainly not hyperactive in the periphery, although there may be adrenergic hypersensitivity.

Whilst the triggering event and resultant neural signalling are usually peripheral, central changes are always generated as well. At spinal level these central changes are suggested by spreading and bilateral sensory phenomena and the occurrence of motor features. There is evidence of evolving changes in thalamic function and involvement of basal ganglia processing. There are changes at cortical level too, with pathological sensori-motor integration within the parietal cortex and cortical reorganization within the primary somato-sensory cortex. These higher level changes may account for features such as 'neglect'.

Investigations on patients with CRPS are often unhelpful diagnostically. Neurophysiological studies may show evidence of a peripheral nerve lesion or denervation that is consistent with the evident peripheral lesion, if present. Radiological studies will exclude structural lesions such as a fracture and arthritis but may show focal or more generalized osteoporosis, probably related to disuse. Isotope bone scanning may reveal a hot spot, but bone and MRI scans have shown very variable features, none of which is diagnostic. Factors such as the type and duration of the syndrome, the degree of immobility, and sequelae from previous treatments often make interpretation difficult and rarely influence management. A normal scan does not exclude a diagnosis of CRPS. However, abnormal haematological or biochemical findings, such as a high erythrocyte sedimentation rate (ESR) or hypercalcaemia, require the diagnosis to be reviewed

Management of these conditions is notoriously difficult and unpredictable. Treatments for neuropathic pain usually seem ineffective. Most invasive interventions, with the possible exception of spinal cord stimulation, have not proved helpful. Intense debate about the role of interrupting the sympathetic nervous system has taken place, and the past few decades have witnessed the gradual demise first of surgical sympathectomy, then neurolytic procedures, and then regional intravenous sympatholytic infusions with guanethidine or other agents. Abandonment of both such procedures and of oral alpha- and beta-blocking drugs has occurred mainly because they are generally ineffective, a fact borne out by various meta-analyses. However, such analyses cannot predict the outcome in an individual patient. The one agreed therapeutic aspect is that restoration of mobility is crucial, although often difficult to achieve on account of pain. Benefits from graded motor imagery techniques and use of a mirror box (see below) have been reported, but their long-term effectiveness is currently uncertain.

There is now a revival of interest in using a short course of oral steroids, and the experimental use of intravenous gamma globulin is being explored. To improve abnormal bone and other musculoskeletal disorders, calcitonin and griseofulvin have been tried and more recently bisphosphonates. Given the possible pseudo-inflammatory changes seen in some patients, vitamin C has been proposed in view of its antioxidant properties, as has the use of topical free-radical scavengers. None of these drugs has been investigated in major controlled studies, nor is any licensed for use in CRPS.

The prognosis for recovery is unpredictable. With time, often measured in years, improvement not infrequently occurs, but when CRPS is long established and florid, the chances of recovery are small.

Painful diseases affecting muscle

Whilst rare in the muscular dystrophies, pain, particularly at rest, is a feature typically encountered in muscle disorders where there is rapid destruction of muscle cells such as in rhabdomyolysis; involvement of intramuscular blood vessels and connective tissues; or defects in muscle energy metabolism. Muscle pain includes not only myalgia, but also painful cramps and contractures. The underlying myopathic disorder may be acute or chronic, focal or generalized, and occur at rest, or during or after exercise.

Focal muscle pain may require consideration not only of a local lesion of the muscle itself (e.g. the very rare intrinsic tumour), but much more commonly pain due to muscle involvement secondary to upper motor neurone disorders (e.g. painful spasms), radicular causes and ischaemia (e.g. compartment syndromes). Local soft tissue lesions (e.g. arthritis, bursitis) which can mimic a focal muscle disorder sometimes also need to be excluded.

Some important examples of generalized painful disorders of muscle are summarized in Table 22.14.

Muscle pain is signalled by sensory afferents whose free endings are mainly near small blood vessels. The absence of these endings around muscle fibres themselves probably explains the paradoxical lack of pain in conditions such as muscular dystrophies, despite even massive muscle destruction. The sensory nerves innervating muscle are classified into Group III, thinly myelinated fibres corresponding to cutaneous Aδ fibres and conducting at 3–13 m/s, and Group IV fibres corresponding to cutaneous C fibres, conducting at 0.6–1.2 m/s. The nociceptor endings respond to various pain-producing (algesic) substances in muscle, and particularly important receptors may include purinergic receptors activated by ATP, and receptors which are sensitive to protons and hence low pH. Both increased levels of ATP and low pH are associated with many painful conditions of muscle, but contrary to expectation, lactate is unlikely to be important in pain from muscle ischaemia. Transduction of mechanical stimuli probably involves one or more acid-sensitive ion channels,

Table 22.14 Some painful disorders associated with muscle.

Polymyalgia rheumatica: age usually >60 years; proximal pain, stiffness and tenderness, particularly around shoulder girdle; raised ESR and CRP. Responds well to steroids. No true weakness; normal CK and EMG; muscle biopsy usually normal or may show interstitial inflammation. Not strictly myopathic but inflammatory/vasculitic; may co-exist with giant cell arteritis
Polymyositis: painful in acute and severe cases, otherwise usually painless, as is inclusion body myositis
Alcoholic myopathy
Myopathic pain, generalized or focal, from viral, bacterial or parasitic infection. Usually transient. Enquire about precipitating infection, particularly viral, and foreign travel
Myopathies of metabolic bone disease: triad of myopathy typically producing a waddling gait, pain (from muscle and/or bone), and brisk reflexes
Myopathies due to certain defects in muscle energy metabolism – usually exercise related: early-onset pain from defect of glycogenolysis and 'second wind' pain (e.g. myophosphorylase deficiency [McArdle's disease]); later-onset pain in patients with defects in lipid oxidation (e.g. carnitine palmitoyl transferase deficiency)
Idiopathic paroxysmal myoglobinurias
Some idiopathic myopathies
Acute and sub-acute drug-induced myopathies: at least 30 drugs and toxins incriminated, including heroin, amphetamine, phencyclidine, statins, vincristine, AZT, cimetidine, drugs producing profound hypokalaemia. Steroid myopathy is nearly always painless

CK, creatine kinase; CRP, C-reactive protein; EMG, electromyogram; ESR, erythrocyte sedimentation rate.

and responsiveness of high threshold mechano-sensitive muscle receptors is increased by the presence of algesic substances. In severe post-exertional pain, with onset after 1–2 days and lasting 5–7 days, the cause of the pain may relate to micro-trauma perhaps with an inflammatory reaction.

Such properties of afferent nerves may explain why muscles become tender, and more so on movement or pressure. The secondary central changes that follow, which are extensive, diffuse and lack the more point-to-point characteristics of sensory afferents from skin, account for clinical phenomena particularly seen when muscle is involved. These phenomena include wide spread of pain outside the local area of damage or disease, referred pain, and also the common clinical phenomenon of reversible sensory symptoms (accompanied by lowered sensory thresholds) in skin overlying the painful muscle, due to central interaction of muscle and skin afferents.

Despite standard investigations for muscle disease, sometimes including muscle biopsy, and rarely more extensive metabolic and other specialized tests, the cause of muscle pain is often not found. Treatment of muscle pain is, where possible, that of the underlying cause. Drug-induced pain is usually reversible when the drug is discontinued.

Fibromyalgia

Distinct from painful myopathies are the numerous tender muscular points which are the hallmark of fibromyalgia, often a vexed diagnosis. The American College of Rheumatology diagnostic criteria comprise widespread pain for at least 3 months, and pain on palpation of at least 11 of 18 specific tender points. Nearly all patients also complain of sleep disturbance and fatigue. Other neurological symptoms including headaches and paraesthesias are common. No definite pathological cause has been found so far, but there is currently no evidence to suggest depression as an aetiology. Many different treatments have been tried, including drugs such as amitriptyline, pregabalin and intravenous lidocaine, acupuncture, exercise and other physical measures, and behavioural techniques. Their efficacy is variable and unpredictable. A multi-disciplinary approach is often the best, but in many patients the condition remains troublesome.

Phantom pain

One of the most curious phenomena within medicine is that whenever a body part is removed, a sensation of the missing part may persist (the phantom sensation) and sometimes there will be pain in that missing part (phantom pain). The subject of much literature, folklore and artistic representation, phantom phenomena have become increasingly studied and their mechanisms investigated. Phantom pain most commonly develops in a missing limb or part of that limb, but phantom teeth, breasts, eyes, genitalia and various viscera have been described. Phantom pain also occurs in a body part that has been denervated but nevertheless remains intact – for instance, the body below a complete or partially transected spinal cord, or an arm denervated following a brachial plexus injury. Because patients often suspect they may be disbelieved or thought insane, phantom sensations including pain are probably under-reported and thus more common than generally appreciated.

Phantom pain in a limb needs to be distinguished from stump pain. In the latter, pain is in the region of the stump, where neuromas (although not necessarily painful) will inevitably be present, sometimes with other abnormal tissues including scars and musculoskeletal changes. There is therefore often a combination of neuropathic and nociceptive pains. Local measures may be needed to try and ease the pain, particularly if there are poorly fashioned skin flaps or local infections. Sometimes surgery is needed, but it is very rarely indicated for pain control itself. Surgery for a neuroma is seldom required unless there are particular circumstances, such as the neuroma being situated where pain is induced by pressure from wearing a prosthesis. This is because removing the neuroma simply results in the formation of one more proximally.

Phantom pain often has certain features:

- It occurs unpredictably in those with missing body parts, particularly when the missing part is distal.
- It is felt in, or within, the area of the missing part.
- The pain varies from the mild to the intolerable. Suicide has occasionally been reported.
- It may have various qualities, e.g. burning, aching, crushing, and gnawing; it can be continuous or intermittent, sometimes with brief paroxysms; and can be influenced by stimulation of other parts of the body, visceral influences such as micturition, and psychological factors. It may be associated with cramps, spasms, painful postures and distortions within the phantom. It is worse if the patient perceives they have no ability to move the phantom, although paradoxically pain may prevent this feeling of being able to move.
- Pain prior to amputation may be a risk factor for the development of phantom pain. The phantom pain may resemble that previous pain.
- When phantom pain is present, the phantom sensation persists.
- With time the area of the phantom sometimes shrinks, particularly its proximal part, and this feature can affect phantom pain as well. This 'telescoping' can give rise to curious phantom phenomena – for instance, a phantom hand may be felt tucked up near the shoulder with nothing intervening.
- It may develop instantaneously, or soon after removal of the part. Occasionally pain may come on months or years later. Phantom pain is often very long-lasting, but sudden resolution rarely occurs spontaneously, and even more rarely after a stroke affecting the phantom area represented in the brain.
- Phantom sensations and pain occur regardless of the cause of loss of the body part, i.e. whether due to trauma, surgical removal or disease. Usually loss of a body part will have been quick, but the same phantom phenomena are described in the slow loss that occurs with leprosy.
- Phantom phenomena including pain are relatively rarely experienced in congenital absence of a limb, or after amputation of a body part in childhood, although childhood phantom pain may be more common than previously thought.
- Some very curious temporal painful phantom phenomena have been reported. For example, phantom lower limbs felt after thoracic spinal cord transaction disappeared when cord compression from a cervical disc developed, only to return when the disc was removed. Conversely and paradoxically, phantom pain in a paraplegic became manifest following spinal anaesthesia.

The treatment of phantom pain is extremely disappointing. Over 68 different types of treatment have been reported, ranging from numerous drugs to neurosurgical and other invasive treatments. Although the use of opioids is being explored further, currently treatment is usually ineffective. Unfortunately preemptive analgesia does not prevent the development of phantom pain. It is hoped that recent studies on neural plasticity may lead to new approaches.

When a body part loses its sensory innervation, changes in somato-sensory cortical and thalamic representation take place. Changes can be very rapid; for example, even an anaesthetic ring block of a finger results in cortical changes within a few minutes. The area of brain from which input has been deprived is physiologically 'invaded' by innervation from adjacent areas. Such phenomena have been studied extensively in humans, and shifts in cortical representation may be more extensive in the presence of pain, normalize with treatment of the pain, and account for peculiar referred patterns of sensation – for instance, a touch on the face being felt in the phantom limb of amputees. The specific role of pain in these phenomena remains to be clarified.

In order to try to modify these neuroplastic changes, graded motor imagery techniques have been tried, as has the mirror box, particularly for patients with a phantom upper limb. A mirror is placed vertically in front of the patient, at right angles to the chest. The patient is asked to mimic the position of the phantom limb with the intact limb, and then to look into the mirror on the side of the intact limb. The patient sees the mirror reflection of the intact hand superimposed on the perceived position of the missing limb. By attempting symmetrical movements of the two limbs, the patient may feel the phantom limb move. Intriguingly, the ability to exert apparent control over the phantom limb can result in pain relief. Beneficial results have been reported with these techniques, but pain relief is unpredictable and may be transient. Further studies are needed.

Management

The most important prelude to management of chronic pain is correct diagnosis. Pain in a patient with a neurological disorder does not necessarily mean that the pain is primarily due to that disorder. In the author's view, by far the most common misdiagnosis is overlooking a complicating, additional or even unrelated musculoskeletal component or cause. Indeed, very often a musculoskeletal cause mimics a neurological condition. Pain due to nociceptive causes is almost always easier to treat than neuropathic pain; this makes exclusion of nociceptive causes particularly important, and avoids inappropriate neurological management.

An example is a sensory disturbance in the forearm, often associated with rather vague numbness and tingling and sometimes hyperalgesia along the posterolateral aspect of the forearm. These symptoms are often attributed to a peripheral nerve lesion or C6 radiculopathy. However, palpation over the lateral epicondyle typically elicits marked discomfort and exacerbation of the symptoms. Treatment of the tender muscular point, possibly some form of tennis elbow, curiously results not only in resolution of the pain but also the sensory features, which, as mentioned above, are mediated by central processes.

Management of nociceptive pain will be dictated by the underlying cause. For example, the finding of tender muscular points, stiffness, pain on active or passive movement, or abnormal posture may well lead to effective treatment, particularly with physical forms of treatment from a physiotherapist or other allied medical practitioner. The same approach will be required in a patient with MS or spinal injury with a spinal deformity resulting from weakness, or the arthritis that commonly accompanies Parkinson's disease. Surgery will be required for a few, specific painful disorders sometimes seen by neurologists, including the osteoid osteoma and glomus tumour discussed earlier.

Management of neuropathic pain

Often the management of neuropathic pain is unsatisfactory, and the evidence base for any particular form of treatment is weak. The methods of treating neuropathic pain, often used in combination, comprise:

- Drugs;
- Neuro-ablative or neuro-stimulation procedures;
- Other physical forms of treatment;
- Psychological approaches to management.

Drugs

The ideal analgesic drug would be one in which the mode of action was precisely tailored to the underlying mechanism subserving the pain. Unfortunately, in any specific patient, there is rarely an effective symptom-related approach to guide therapy, nor a rationale for using any specific drug. Many drugs used do not necessarily produce analgesia, but may reduce abnormal sensations such as hyperalgesia and allodynia.

The mechanisms of actions of drugs used in pain management are more complex than previously thought:

- The once clear-cut division of those drugs that act peripherally and those that act centrally is now less secure. For instance, opiates have peripheral as well as central effects, and anti-inflammatory drugs have central as well as peripheral effects.
- The properties of nerves on which drugs act change in the presence of disease or injury, and the effects of drugs may change. For example, certain sodium channels on sensory afferents are upregulated after nerve injury.

Occasionally, pain management specialists use short-duration intravenous drug challenges to try and predict benefit of a particular class of drug, and sometimes one of these drug challenges will lead to pain relief that long outlasts the duration of action of the drug. These drug challenges include:

- Lidocaine (lignocaine) to predict benefit of sodium-channel blockers such as mexiletine;
- Phentolamine to predict benefit of sympatholytic agents;
- Ketamine to predict benefit of ketamine and other NMDA-blocking agents;
- Opiates to predict benefit of opiates.

Anticonvulsants and antidepressants are the mainstay of drug treatment, and these have been the subject of several meta-analyses. More recently, the use of opiates in non-malignant neuropathic pains has expanded. A huge number of other drugs have been tried, often with little if any evidence of benefit as judged from adequate, appropriately controlled and long-term studies. There is increasing interest in exploring the usefulness of drugs whose efficacy might be predicted from mechanisms mediating pain, for instance, those with effects on NMDA receptors (e.g. ketamine) and on the TRPV1 receptor (e.g. cannabis and synthetic cannabinoids). However, with the exceptions of gabapentin, pregabalin and duloxetine, and carbamazepine for trigeminal neuralgia, none of these is licensed in the UK for management of pain, and patients should be informed of this. With many drugs, but particularly tricyclic antidepressants, patients need to be warned about the risk of drowsiness in respect of driving and potentially hazardous occupations. To reduce the chance of side effects, the key to any success is to start with a very low dose, often given at bedtime, and increase very slowly. Combination therapy, using drugs with different modes of action, e.g. gabapentin and morphine, has also been advocated for peripheral neuropathic pain. Antidepressants and anticonvulsants are the first drugs to try. Although there is no evidence favouring one or other group in respect of efficacy or side-effects, there is a clinical impression that the anticonvulsants may be better tolerated, particularly in the elderly.

Antidepressants

Antidepressants may be effective in peripheral and central neuropathic pain states.

Tricyclic antidepressants, particularly those with mixed effects on noradrenaline and serotonin, are probably superior to selective serotonin re-uptake inhibitor (SSRI) antidepressants, although there may be no benefit in painful HIV neuropathy. There is little evidence to support one drug being superior to another, although more data are available for amitriptyline. The efficacy of tricyclic antidepressants may also be related to their important local anaesthetic effects, probably through blocking voltage-gated sodium channels. Duloxetine, a dual serotonin and noradrenaline re-uptake inhibitor, has been licensed for treatment of painful diabetic peripheral neuropathy, but should be discontinued if there has been no benefit after 2 months.

The dose of a drug used is typically lower than that used for depression, e.g. amitriptyline, starting at 10 mg nocte, building up by 10 mg weekly to 50–70 mg nocte. Benefit is usually apparent within a few days or weeks, and is unrelated both in time and efficacy to the drug's psychotropic properties. If there is no benefit after 2–3 months, it is appropriate to withdraw the drug slowly. Measurement of drug levels has been used in an attempt to correlate dosage with efficacy but is rarely undertaken in practice.

Anticonvulsants

Almost all anticonvulsants have been used to try to manage neuropathic pain, but benefits are unpredictable. Their use in treating trigeminal neuralgia is considered elsewhere. Lamotrigine has been found to have little benefit in peripheral neuropathic pain, and despite various reports of benefit from drugs such as valproate, levetiracetam and topiramate, efficacy remains to be established in more major studies. In the UK, the majority of these drugs remain unlicensed for treatment of pain.

- Carbamazepine is the treatment of choice, not only in trigeminal neuralgia, but in any other truly neuralgic pain in which there is a brief, severe, stabbing component. Thus, it may be effective for glossopharyngeal and other neuralgias, paroxysmal pain of MS, and tabetic lightning pain. It may be effective for painful diabetic neuropathy, but is usually ineffective for CPSP and other neuropathic pain.
- Gabapentin may be helpful for neuropathic pain; it is only licensed for peripheral neuropathic pain. Somnolence is usually the dose-limiting side effect.
- Pregabalin, related to gabapentin, has been licensed for both peripheral and central neuropathic pains. Preliminary evidence suggests it might be more effective than gabapentin. It has the advantage of an easy twice daily dose regimen; again somnolence may be troublesome but might be a useful feature in patients with difficulty in sleeping.

Different anticonvulsants may involve effects on abnormal neural excitability through effects on different ion channels, such as voltage-gated sodium channels (e.g. carbamazepine) or the $\alpha 2\delta$ voltage-gated calcium channel subunit (e.g. gabapentin – which, despite its name, is not involved with GABA-mediated mechanisms).

Mexiletine

This drug acts as an oral local anaesthetic, but evidence for its efficacy in neuropathic pain has been conflicting. Bradycardia and heart block are contraindications.

Opiates

Opiates are increasingly used for non-malignant and other neuropathic pains. Guidelines on their use are published by the British Pain Society. For example, oxycodone and tramadol may be useful for post-herpetic neuralgia, and methadone may occasionally have a place. The use of opiates in non-malignant pain has been controversial and is greatly complicated by issues concerning dependency and addiction, misuse, legal constraints (in some countries), and even cost. There are also other potential issues, such as possible reduction in testosterone levels when some opioids are used long-term. Because of these issues it is usually wise for long-term opiate therapy to be instituted by a specialist in pain management, and then in a shared-care arrangement with the patient's general practitioner.

Cannabinoids

Despite their effects on the vanilloid receptor involved in nociception, there is at present conflicting evidence whether cannabinoids are useful in chronic neuropathic pain. Trials have been carried out in patients with MS and brachial plexus lesions but, as with so many pain-relieving agents, claims of benefit are difficult to evaluate. Furthermore, cannabinoids, which comprise a number of different components, have psychotropic properties, and may also affect spasticity. Further trials are pending, but currently, whilst a cannabinoid is licensed in Canada for use in pain, cannabinoids remain unlicensed in the UK.

Ketamine and other NMDA-blocking agents

Attempts have been made to block NMDA-mediated processes thought to subserve pain caused by central hyperexcitability. Memantine appears ineffective, but occasional patients respond to subcutaneous or oral ketamine. Amantadine and dextromethorphan have also been used. Ketamine should only be prescribed by specialists in pain management.

Topical agents

There is evidence supporting the use of 5% lidocaine patches, recently licensed in the UK for the treatment of post-herpetic neuralgia. Capsaicin cream, licensed for treatment of post-herpetic and diabetic neuropathic pains, may be useful, but side effects including burning and stinging at the site of application often occur, and great care has to be taken to avoid contact with the eyes.

Botulinum toxin

Botulinum toxin may have pain-relieving properties in addition to those resulting from treatment of muscle spasm and abnormal posture. Pain relief can occur well before, and outlast, improvement in these musculoskeletal components. There have been anecdotal reports of pain relief in various other disorders including post-herpetic neuralgia, migraine and chronic facial pain. Botulinum toxin does not seem to improve acute pain, and the role of this toxin in relief of pain is uncertain. There is experimental evidence that, apart from effects on acetylcholine, the toxin blocks release of substance P, release of glutamate and other neurotransmitters involved in sensory processing.

Intrathecal drugs

Several drugs have been used intrathecally for pain management. These include baclofen especially for central pain, clonidine, opioids and, most recently, ziconotide. Phenol has also been used, but as a neurolytic agent. The evidence base is poor, benefit unpredictable, and this form of treatment should only be carried out in specialized pain management units.

Neuro-ablative and neuro-stimulation procedures

Neuro-ablative procedures

Over the past century, except in the treatment of trigeminal neuralgia, there has been a steady decline in neurosurgical and other procedures designed to interrupt pain pathways, particularly in those whose pain has a non-malignant cause. Apart from the risks of the procedure itself and of causing damage affecting other neurological functions, even successful procedures may result in sensory loss that can be painful (termed 'anaesthesia dolorosa' after somatic nerve lesioning, and 'sympathalgia' after sympathectomy). Furthermore, paradoxically pain will often return, sometimes after a long interval, although obviously this is less important in management of those painful malignant conditions in which life expectancy is short. These sequelae are due to a variety of often poorly understood adaptive central phenomena.

Certain destructive procedures are still occasionally performed, for instance DREZ lesions for treatment of pain from spinal cord injury or brachial plexus lesions discussed earlier. Here too the evidence base for their efficacy is frequently poor. The same reservations apply to destructive chemical procedures. The use of phenol and other neurolytic chemicals applied around nerve roots or intrathecally is rarely undertaken, apart from treating spasticity and its accompanying pain. Phenol applied peripherally can induce further pain (phenol neuritis).

Neuro-stimulation procedures

Every part of the somato-sensory nervous system has been stimulated to try and relieve pain, but apart from transcutaneous electric nerve stimulation (TENS), these techniques are complex and are only carried out in specialized centres. Much of the rationale for stimulation procedures is based on the seminal paper by Melzack and Wall (1965) that led to the gate control theory of pain. This paper, which reported physiological experiments on dorsal root potentials in rats, gave rise to the novel concept that stimulation of large afferent fibres might inhibit (gate) the activity of small diameter, pain subserving fibres in the dorsal horn of the spinal cord, and possibly elsewhere. Although the subject of heated controversy, the paper led to the development of various techniques that provide innocuous neural stimulation, with the aim of alleviating pain.

Transcutaneous electrical nerve stimulation

This involves applying electrodes to the skin with an interposed gel or other appropriate contacting substance. The electrodes are usually placed either side of the painful area, and are attached via wires to a small battery-operated stimulation unit. Impulses can be of variable frequency and intensity, the parameters being selected by the patient usually so as to cause non-painful tingling sensations. Stimulation can be continuous, intermittent or in bursts, and applied for minutes, hours or days. Side effects are infrequent and minor, usually comprising skin irritation beneath the electrodes. Contraindications include open or infected skin, pregnancy (other than in labour), and the presence of a pacemaker. TENS is useless and can cause burns if applied to anaesthetic skin. Benefit is unpredictable, and may only develop some time after stimulation. Some pains may be transiently worsened, particularly if there is tactile allodynia. Controlled trials are obviously difficult, but the technique is simple, safe and cheap, and patients can obtain devices over the counter.

The mechanism of action may include segmental inhibition at the dorsal horn, distinct from painful counter-irritation (pain inhibiting another pain) in which there is diffuse noxious inhibitory control (DNIC) through ascending and descending pathways.

Peripheral nerve stimulation

Implanting stimulating electrodes around a peripheral nerve to obtain pain relief is rarely undertaken now.

Spinal cord stimulation

An electrode is implanted percutaneously or at open operation so as to stimulate the spinal cord by means of electrical stimuli provided by a pulse generator. The aim is to stimulate the posterior columns, but this stimulation is probably not its only mode of action which remains ill understood. One of its most useful indications is angina; other good indications are said to include CRPS, neuropathic pain secondary to peripheral nerve damage or lumbar or cervical spine surgery, and post irradiation and partial traumatic brachial plexus lesions. Up-to-date recommendations for best clinical practice, details of conditions that may or may not respond, contraindications, technical details and a literature review are well set out in a consensus document from the British Pain Society and the Society of British Neurological Surgeons.

Deep brain stimulation

This highly specialized technique originated from two startling discoveries: in humans, stimulation of the fornix and septal regions during psychosurgery produced analgesia; and in rats, stimulation of the central midbrain grey matter allowed them to be operated on without an anaesthetic. The three areas most frequently targeted include the peri-aqueductal grey matter, periventricular grey matter and the somato-sensory nuclei of the thalamus. Whilst experimental pain relief has been attributed predominantly to stimulation of endogenous opioid systems at the first two sites, and stimulation of inhibitory pathways at the third, the underlying mechanisms in humans remain unclear. Debate continues on many aspects, including the indications for deep brain stimulation (probably patients with constant, burning or aching neuropathic pain unresponsive to other measures), appropriate targets and stimulation parameters.

Motor cortex stimulation

This counter-intuitive procedure involves the extradural placement of electrodes over the motor cortex. Pain relief is thought to be subserved by effects on descending inhibition, in turn mediated by sensory nerves present in the motor cortex. Recently, repetitive transcranial magnetic stimulation over the motor cortex has been reported to provide analgesia in patients with central pain and trigeminal neuralgia, an effect that might usefully predict benefit from long-term motor cortex stimulation.

Other physical methods of treatment

Many treatment modalities are used, including different forms of physiotherapy for nociceptive pains, and treatment is usually carried out by physiotherapists, occupational therapists and other allied therapists such as osteopaths and chiropractors. TENS is one such procedure and has been discussed earlier. Another technique often used for musculoskeletal and other pains, and a form of peripheral stimulation, is acupuncture.

Acupuncture

Acupuncture, the insertion of needles into the body for pain relief, has been used for 5000 years. Various techniques are employed:

- Needle stimulation of local points in painful areas, such as for treatment of tennis elbow.
- Needle stimulation of distant points, sometimes multiple and sometimes situated along classic Chinese acupuncture lines. The importance of classic acupuncture points, however, is doubtful.
- Needle(s) may be simply inserted, repetitively rotated, or stimulated electrically, and they may be inserted to different depths.
- Treatment is often given for about 30 minutes, but the optimum duration is unclear.

Acupuncture has been used in treatment of both acute and numerous chronic painful and other disorders. It is most commonly and perhaps effectively used for musculoskeletal rather than neuropathic pain; contraindications include local skin lesions, anticoagulation and pregnancy. Side effects are infrequent, but infection, bleeding, syncope, paraesthesias and, depending on the site and depth of needle insertion, pneumothorax and other internal complications may very rarely occur. Attempts have been made to undertake controlled trials of efficacy using specially adapted needles, but in practice acupuncture is usually given on a trial and error basis.

Despite its potential for placebo effects, acupuncture provides a form of powerful peripheral stimulation. The physiological basis underpinning acupuncture is complex, and includes effects mediated by release of endogenous opioids, not least because analgesia can be reversed by naloxone. Acupuncture also induces both segmental and supraspinal descending inhibitory effects.

Acupuncture carried out for prolonged periods and in a way to cause pain raises the pain threshold and can induce analgesia. This acupuncture-induced analgesia, different from treatment of pain, is a method for allowing surgery to take place without general anaesthesia.

Psychological approaches to management of chronic pain

The psychological components of pain are extraordinarily complex, but the tendency to assume that pain intensity correlates with perceived pain severity can easily be disproved. Rather than being closely linked to sensory dysfunction, from the psychological perspective it is the affective, cognitive, behavioural and social aspects for the patient as well as the family that are crucial. As consistently shown by functional imaging, magnetoencephalography and other investigative tools, non-sensory brain changes occur alongside the sensory phenomena that characterize acute and chronic pains. Structures, particularly including the anterior cingulate, prefrontal cortex and insula, are implicated in encoding pain affect. It is thus increasingly recognized that any firm division between psychological and somato-sensory aspects of pain is probably meaningless.

Currently, normal psychological aspects of pain are thought to comprise four concepts: attention, catastrophizing, avoidance and depression. The neurophysiological bases underlying these are starting to be investigated. Building on these concepts and coinciding with the decrease in invasive procedures, there has been a rapid increase in the use of psychological strategies for management of neuropathic pain.

Patient management falls to pain psychologists, the majority of whom work as members of a multi-disciplinary pain management team. It is important for the patient to accept that pain psychologists are concerned with management and not cure of the pain. Individual psychologists tend to have expertise in one or more specific therapeutic approaches, and whilst it is difficult to compare different forms of psychological intervention, cognitive behavioural therapy (CBT) is one of the most widely used techniques that meta-analyses have shown to be effective. In-patient management for selected patients may be particularly beneficial.

Psychiatric treatment may also be required. It is usually unwise to attribute chronic pain to a psychological cause, and patients with significant depression will need appropriate treatment and when necessary referral to a psychiatrist. Malingering as a cause of chronic pain is well recognized but very rare.

The placebo phenomenon

The placebo phenomenon in treating pain encapsulates the concept that the individual believes that receiving an effective analgesic treatment can reduce pain. Although it is often stated that one-third of beneficial responses to inert analgesic drugs are due to placebo, the range varies from 0 to 100% of patients. Cultural, experiential, experimental and numerous other factors are relevant. Often thought that pain relief following an inert substance was due to imagination or a psychological sleight of hand, there is compelling evidence that placebo effects have a physiological basis. This evidence, from acute pain studies, includes findings that:

- Placebo ultrasound can reduce pain and swelling after tooth extraction.
- Naloxone can reverse placebo, suggesting opioid mechanisms are important, although naloxone can also produce hyperalgesia that can offset the placebo effect.
- Placebo analgesia is associated with changed patterns of cerebral blood flow similar to those seen with opioids.
- Functional MRI evidence suggests that placebo decreases activity in pain-subserving brain regions; conversely, during anticipation of pain, brain activity increases in prefrontal cortex.

- Placebo analgesic effects, including physiological phenomena, are seen following technically abortive surgery, even when the patient is under general anaesthesia and therefore unaware.
- Placebo is a phenomenon also seen in treatment of other, non-painful and chronic disorders, including Parkinson's disease, Alzheimer's disease and depression.

The placebo phenomenon is proving to be an intriguing and important phenomenon in pain and other conditions, and the mechanisms are likely to include those subserving expectancy and desire. Although pain relief by means of placebo would appear to be an ideal outcome, there are major ethical considerations when using placebo in clinical practice and in clinical trials. Current views are controversial, but the prevailing consensus is that patients should not receive placebo without consent, even if that consent includes placebo being one of a number of treatment options offered.

Absence of pain

Patients may not experience pain, either because there is a defect in sensory pathways, insensitivity to pain or, extremely rarely, due to lack of concern in response to a normally received stimulus, indifference to pain.

Insensitivity to pain

In these conditions, stimuli that would normally be painful are not transmitted to the brain. This lack of pain input may be congenital and occurs in some rare hereditary small fibre neuropathies, notably, but not exclusively, HSAN Type IV (see below). Patients with this autosomal recessive neuropathy develop serious painless injuries amongst other defects, and have absence of unmyelinated peripheral axons, small sensory neurones in the dorsal root ganglia, and Lissauer's tracts. The mechanisms for the lack of pain perception may relate to mutations in the *TrkA* gene that encodes the high affinity receptor for NGF, which in turn is crucial for development of nociceptive and sympathetic neurones.

Acquired causes include occasional cases of diabetes, syphilitic tabes dorsalis, and lesions interrupting second-order central crossing spinothalamic fibres as seen in syringomyelia. As a result of the lack of protective innervation, patients may develop painless scars, burns and ulcers, inadvertently bite their tongue and otherwise self-mutilate, and have disorganized (Charcot's) joints, and osteomyelitis. Such injuries need to be contrasted with the self-mutilation that can occur in association with anaesthesia dolorosa, in which the positive sensory disturbances (possibly including itch) give rise to constant scratching and damage, the human equivalent of autotomy in animals.

Indifference to pain

In congenital indifference to pain (also known as asymbolia for pain, congenital pure analgesia, congenital universal insensitivity to pain), patients appear to have absent pain recognition which dates from birth. They do not react to painful stimuli anywhere over the body, but other sensory modalities and reflexes seem to be normal. They sustain painless injuries including skin lesions and fractures dating from childhood. Autosomal dominant and recessive families have been reported. In some patients insular damage perhaps leading to sensory-limbic disconnection has been reported, but in most patients no consistent pathological abnormalities have been found in either the peripheral or central nervous system. The cause of these very rare disorders remains unknown, although the clinical features recall those patients with other conditions in which medial pain-subserving circuits may well be implicated – for example, patients with frontotemporal dementia, and patients who in previous decades had a frontal lobotomy for treatment of intractable pain. However, it is now evident that, in some patients, their supposed indifference to pain is due to impaired function of the voltage-gated sodium channel gene *SCN9A*, and is in reality a channelopathy-associated insensitivity to pain.

Transient indifference to pain

It has long been noted that in acute situations in which pain would be expected, quite paradoxically pain may not be experienced at all. Classic studies came from Beecher who described this phenomenon in battle-injured soldiers in the Second World War, but the same phenomenon has been documented in other wartime situations and in occasional patients with very severe injuries admitted to a hospital A&E department. This analgesia is short-lived and localized to the site of injury. The mechanisms are thought to include stress-induced release of endorphins and massive cortical and spinal inhibitory processes. Perhaps having a similar basis is the impaired pain perception in those patients with parasomnias who sustain injuries during sleep-related violence. Pain appreciation is also impaired as a result of the transient effects of drugs such as opiates.

Conclusions

There has been an explosion of knowledge about how pain is detected and processed by the nervous system and how pain impacts on those who experience it. This knowledge extends from molecular mechanisms at the peripheral nociceptor endings to neural networks at the cortical level. But the management of pain remains in its infancy, and some would argue that there have been rather few major therapeutic advances in the past century. Paradoxically, rather than neurologists, it has been two physicians in other disciplines who have contributed most to alleviating patients' pain, and whose contributions serve as beacons for the future. One pioneer was John Bonica, an anaesthetist who envisaged the concept of pain as a multidisciplinary speciality and who with others initiated the International Association for the Study of Pain. The other was Dame Cicely Saunders, founder of the modern hospice movement, who at the age of 85 quoted so aptly: 'there's so much more to be learned about pain'.

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23

Autonomic Dysfunction

Christopher Mathias

The last 25 years have seen major advances in the recognition, investigation and treatment of a variety of disorders that cause or contribute to autonomic dysfunction. This has been a result of many factors. Many clinicians consulted by patients with symptoms that cannot be explained now consider autonomic disorders as a possible cause. Advances in non-invasive technology have resulted in more accurate and reproducible methods of investigation, thus aiding diagnosis, understanding pathophysiological mechanisms and enabling targeted therapy for autonomic dysfunction. Collaboration between specialties within neurology, such as with movement disorders groups and with other medical disciplines such as diabetology and cardiology, has been helpful in understanding autonomic involvement in common neurological and medical diseases. Advances in basic science have enabled neurological repair, e.g. in the spinal cord, and have refocused attention on the many autonomic abnormalities that occur in patients with spinal cord injuries. Finally, new autonomic disorders have been described, examples being dopamine beta hydroxylase deficiency (DβH), immune disorders affecting autonomic ganglia and the postural tachycardia syndrome (PoTS); and in the latter its close association with the joint hypermobility (Ehlers–Danlos III) syndrome.

Autonomic investigation units began to be established in UK during the 1970s. Their scope of activity varied, depending much upon research funding. Established units have seen exponential growth in clinical service and research activity, which have advanced greatly the recognition, investigation and management of autonomic disorders. Activities now encompass a wide range of disorders, from autonomic failure syndromes to common disorders such as parkinsonian syndromes, hyperhidrosis and neurally mediated syncope. This chapter summarizes our usual diagnostic approach and the range of tests and treatments available.

Classification of autonomic dysfunction

The autonomic nervous system has cranio-sacral parasympathetic and thoraco-lumbar sympathetic pathways (Figure 23.1) and supplies every organ in the body. The system influences target organ function locally and also operates more centrally, i.e. it controls vital functions such as arterial blood pressure and body temperature. Specific neurotransmitters in each pathway influence ganglionic and post-ganglionic activity (Figures 23.2 and 23.3). Autonomic diseases thus may occur with lesions or dysfunction at different sites of the neural axis, in the brain, spinal cord or periphery.

Autonomic disorders may be classified in a variety of ways. One approach is to divide them into localized and generalized disorders. Localized disorders affect an organ or region of the body but they may be part of generalized disease, such as gustatory sweating in diabetes mellitus (Table 23.1).

Generalized disorders often affect systems, such as those involved in blood pressure control and thermoregulation. They can be primary when the cause is often unclear, or secondary when associated with a specific disease or its complications (Table 23.2).

Drugs are a common cause of autonomic dysfunction, either because of their pharmacological effects or because of autonomic nerve damage (Table 23.3). Damage to the autonomic nervous system often causes irreversible abnormalities. This contrasts with intermittent autonomic dysfunction, the common transient abnormalities that generate so much morbidity. These conditions include neurally mediated syncope, PoTS and essential hyperhidrosis.

Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

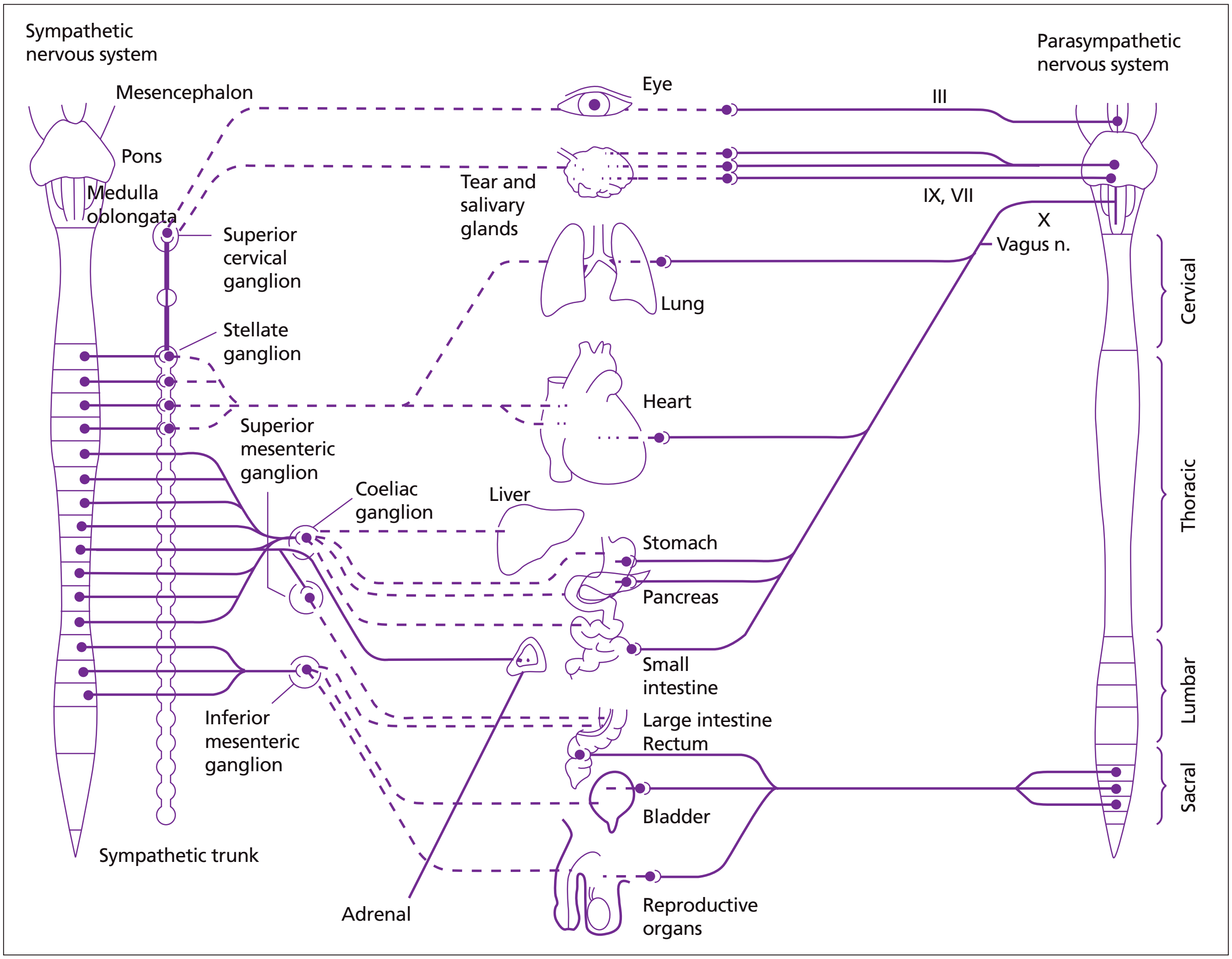
Sympathetic nervous system
Mesencephalon
Pons
Medulla oblongata
Superior cervical ganglion
Stellate ganglion
Superior mesenteric ganglion
Coeliac ganglion
Inferior mesenteric ganglion
Sympathetic trunk
Adrenal
Eye
Tear and salivary glands
Lung
Heart
Liver
Stomach
Pancreas
Small intestine
Large intestine
Rectum
Bladder
Reproductive organs
Parasympathetic nervous system
III
IX, VII
X
Vagus n.
Cervical
Thoracic
Lumbar
Sacral

Figure 23.1 Scheme outlining details of the cranio-sacral parasympathetic and thoraco-lumbar sympathetic outflow to various target organs. (From Janig & McLachlan 2002, with permission.)

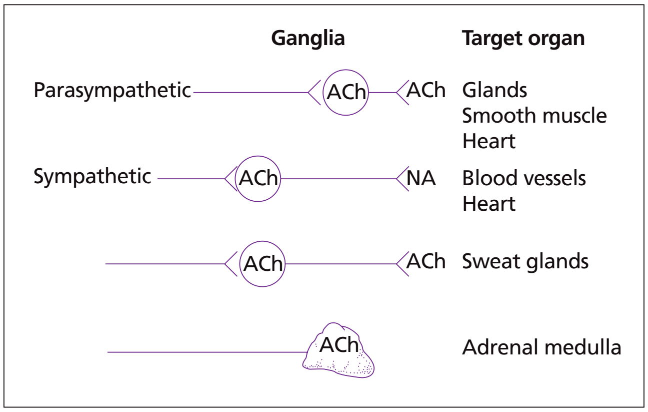
Ganglia
Target organ
Parasympathetic
ACh
ACh
Glands
Smooth muscle
Heart
Sympathetic
ACh
NA
Blood vessels
Heart
ACh
ACh
Sweat glands
ACh
Adrenal medulla

Figure 23.2 Outline of the major transmitters at autonomic ganglia and post-ganglionic sites on target organs supplied by the sympathetic and parasympathetic efferent pathways. The acetylcholine receptor at all ganglia is of the nicotinic subtype. Ganglionic blockers such as hexamethonium thus prevent both parasympathetic and sympathetic activation. However, atropine acts only on the muscarinic (ACh-m) receptor at post-ganglionic parasympathetic and sympathetic cholinergic sites. The co-transmitters along with the primary transmitters are also indicated (ACh, acetylcholine; NA, noradrenaline). After Mathias (1998).

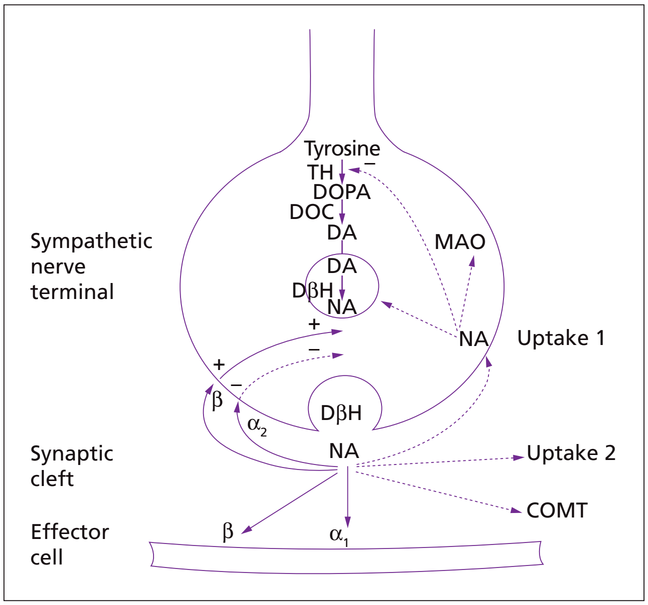

Figure 23.3 Steps involved in the formation of noradrenaline (NA) from tyrosine within a sympathetic nerve terminal (DA, dopamine; DβH, dopamine beta hydroxylase; DDC, dopadecarboxylase; DOPA, dihydroxyphenylalanine; TH, tyrosine hydroxylase). NA in granules is released by a process of exocytosis into the synaptic cleft, following which it acts on various alpha or beta adrenoreceptors, either pre- or post-synaptically. NA is subject to various processes which involve uptake 1 into the nerve terminal, following which it is either incorporated into granules, exerts negative feedback on TH or is metabolized by monoamine oxidase (MAO). Some is taken up into non-neuronal tissues (uptake 2), some metabolized by catechol-*O*-methyltransferase (COMT), while the rest spills over into the circulation. From Mathias (2004) with permission.

Table 23.1 Examples of localized autonomic disorders.

Horner's syndrome
Holmes–Adie pupil
Crocodile tears (Bogorad's syndrome)
Gustatory sweating (Frey's syndrome)
Reflex sympathetic dystrophy
Idiopathic palmar or axillary hyperhidrosis
Chagas disease (*Trypanosoma cruzi*)*
Surgical procedures†
Sympathectomy (regional)
Vagotomy and gastric drainage procedures in 'dumping' syndrome
Organ denervation following transplantation (heart, lungs)

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* Listed here because the disease targets specifically intrinsic cholinergic plexuses in the heart and gut.

† Surgery also may cause other localized disorders, such as Frey's syndrome after parotid surgery.

Table 23.2 Outline classification of autonomic disorders.

Primary

Acute/subacute dysautonomias
Pure pan-dysautonomia
Pan-dysautonomia with neurological features
Pure cholinergic dysautonomia

Chronic autonomic failure syndromes
Pure autonomic failure
Multiple system atrophy (Shy–Drager syndrome)
Autonomic failure with Parkinson's disease

Secondary

Congenital
Nerve growth factor deficiency

Hereditary
Autosomal dominant trait
Familial amyloid neuropathy

Autosomal recessive trait
Familial dysautonomia – Riley–Day syndrome
Dopamine beta hydroxylase deficiency

Metabolic diseases
Diabetes mellitus
Chronic renal failure
Chronic liver disease
Alcohol-induced

Inflammatory
Guillain–Barré syndrome
Transverse myelitis

Infections
Bacterial – tetanus
Viral – HIV infection

Neoplasia
Brain tumours – especially of third ventricle or posterior fossa
Paraneoplastic, especially adenocarcinoma of lung and pancreas

Surgery
Vagotomy and drainage procedures – 'dumping syndrome'

Trauma
Cervical and high thoracic spinal cord transection

Drugs, chemical toxins (see also Table 23.3)
By direct effects
By causing a neuropathy

Neurally mediated syncope
Vasovagal syncope
Carotid sinus hypersensitivity
Situational syncope

Postural tachycardia syndrome

Table 23.3 Drugs, chemicals, poisons, and toxins causing autonomic dysfunction.

Decreasing sympathetic activity

Centrally acting
Clonidine
Methyldopa
Moxonidine
Reserpine
Barbiturates
Anaesthetics

Peripherally acting
Sympathetic nerve endings (guanethidine, bethanidine)
α-Adrenoceptor blockade (phenoxybenzamine)
β-Adrenoceptor blockade (propranolol)

Increasing sympathetic activity
Amphetamines
Releasing noradrenaline (tyramine)
Uptake blockers (imipramine)
Monoamine oxidase inhibitors (tranylcypromine)
β-Adrenoceptor stimulants (isoprenaline)

Decreasing parasympathetic activity
Antidepressants (imipramine)
Tranquillizers (phenothiazines)
Antidysrhythmics (disopyramide)
Anticholinergics (atropine, probanthine, benztropine)
Toxins (botulinum)

Increasing parasympathetic activity
Cholinomimetics (carbachol, bethanechol, pilocarpine, mushroom poisoning)
Anticholinesterases
Reversible carbamate inhibitors (pyridostigmine, neostigmine)
Organophosphorous inhibitors (parathion, sarin)

Miscellaneous
Alcohol, thiamine (vitamin B_1) deficiency
Vincristine, perhexiline maleate
Thallium, arsenic, mercury
Mercury poisoning (pink disease)
Ciguatera toxicity
Jellyfish and marine animal venoms, scombroid posioning
First dose of certain drugs (prazosin, captopril, propranolol)
Withdrawal of chronically used drugs (clonidine, opiates, alcohol)

Table 23.4 Some clinical manifestations of autonomic dysfunction.

Cardiovascular	
Postural hypotension	Supine hypertension
Lability of blood pressure	Paroxysmal hypertension
Tachycardia	Bradycardia
Sudomotor	
Hypohidrosis or anhidrosis	Hyperhidrosis
Gustatory sweating	
Hyperpyrexia	Heat intolerance
Alimentary	
Xerostomia	Dysphagia
Gastric stasis	Dumping syndromes
Constipation	Diarrhoea
Urinary	
Nocturia	Frequency
Urgency	Incontinence
Retention	
Sexual	
Erectile failure	Ejaculatory failure
Retrograde ejaculation	
Eye	
Pupillary abnormalities	Ptosis
Alachryma	Abnormal lachrymation with food ingestion

Clinical features

Clinical features of autonomic disease cover a wide spectrum (Table 23.4) and result from underactivity or overactivity. The history is of particular importance in consideration and recognition of autonomic disease and in distinguishing dysfunction from other disorders.

In brief:

- Sympathetic adrenergic failure causes orthostatic (postural) hypotension and ejaculatory failure in the male;
- Sympathetic cholinergic failure causes anhidrosis;
- Parasympathetic failure causes dilated pupils, fixed heart rate, sluggish urinary bladder, atonic large bowel and, in the male, erectile failure.

The extent of dysfunction is dependent on the degree of autonomic damage. With autonomic hyperactivity, the reverse occurs. In some disorders, particularly in neurally mediated syncope, there may be a combination of over-activity and under-activity, with bradycardia caused by increased parasympathetic activity and hypotension brought about by withdrawal of sympathetic activity.

Autonomic disease may present in any age group. At birth it is seen in the rare condition familial dysautonomia (Riley–Day syndrome), in teenage years in the common disorder vasovagal syncope and between the ages of 30 to 50 in familial amyloid polyneuropathy (FAP). Neurodegenerative disorders affecting the autonomic nervous system often occur after the age of 50 years.

The majority of autonomic diseases are sporadic. However, genetically transmitted disorders include the Riley–Day syndrome and FAP. There often is a family history in vasovagal syncope, especially in those presenting below the age of 20 years. Drug-induced autonomic disease may be caused by impaired metabolism or the production of toxic metabolites, as with perhexiline maleate neuropathy. A detailed history relating to drug usage, chemical and toxin exposure is always necessary (Table 23.3).

Autonomic involvement, even if it affects only a single organ or system (Table 23.5), may be an important feature of an underlying disease. For example, Horner's syndrome, with mainly cosmetic effects, may be the harbinger of underlying non-autonomic disease (such as apical tuberculosis or lung neoplasm in Pancoast syndrome). The usually benign Holmes–Adie pupil may occur in isolation, or with absent tendon reflexes and other autonomic features, such as an afferent baroreceptor defect causing orthostatic hypotension and labile hypertension, sweating abnormalities and a dry cough (Holmes–Adie syndrome). In generalized disorders such as multiple system atrophy (MSA), a single system may be involved initially. Thus, erectile failure in the male, constipation or urinary bladder dysfunction in either gender can pre-date other autonomic or neurological features. The clinical features are now considered under each major system.

Table 23.5 Some clinical manifestations in patients with pure autonomic failure.

Cardiovascular system	Orthostatic (postural) hypotension
Sudomotor system	Anhidrosis, heat intolerance
Alimentary tract	Xerostomia, oro-pharyngeal dysphagia, constipation, occasionally diarrhoea
Urinary system	Nocturia, frequency, urgency, incontinence, retention
Reproductive system	Erectile and ejaculatory failure (in the male)
Respiratory system	Stridor, involuntary inspiratory gasps, apnoeic periods
Ocular	Alacrima, aniscoria, Horner's syndrome
Other neurological features	Parkinsonian, cerebellar and pyramidal signs

Oropharyngeal dysphagia, incontinence and respiratory features, along with additional neurological features suggest multiple system atrophy.

Cardiovascular system

Orthostatic hypotension

Symptoms of orthostatic hypotension are often the reason for requesting medical advice and may provide initial clues to underlying autonomic disease. Orthostatic or postural hypotension is defined as a fall in blood pressure of 20 mmHg systolic or 10 mmHg diastolic on sitting, standing or during 60° head-up tilt (Figures 23.4 and 23.5). In neurogenic orthostatic hypotension, levels of plasma noradrenaline do not rise when upright, as occurs in normal subjects (Figure 23.6), the lack of rise reflecting impaired sympathetic activity. Hypoperfusion of organs, especially above heart level such as the brain, cause the malaise, nausea, dizziness and visual disturbances that often precede loss of consciousness (Table 23.6).

The fall in blood pressure and associated symptoms during postural change often varies within the same individual. If blood pressure falls precipitously, syncope tends to occur instantly and is likely to cause injury. Occasionally, seizures may occur as a result of cerebral hypoxia in syncope. With time and frequent exposure to orthostatic hypotension, some come to tolerate a low cerebral perfusion pressure with few or even no symptoms, presumably because of improved cerebrovascular autoregulation.

A variety of symptoms result from hypoperfusion elsewhere. Neck pain in a coat-hanger distribution (suboccipital and shoulder regions) differs from other types of neck pain by developing when upright. It is relieved by sitting or lying flat, when the blood

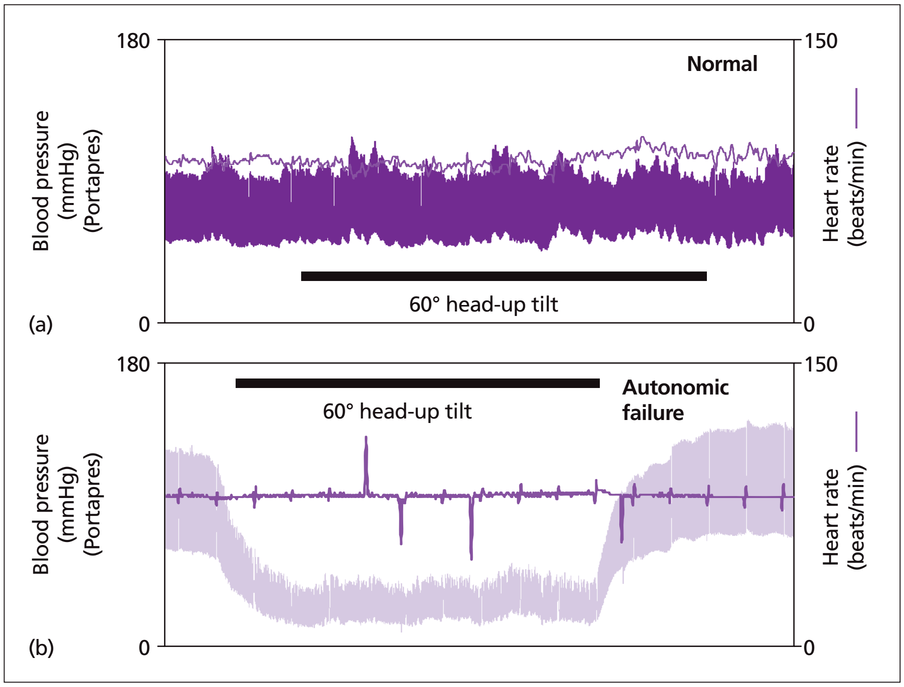


Figure 23.4 Blood pressure and heart rate before, during and after head-up tilt in (a) a normal subject, and (b) a patient with autonomic failure. In the normal subject there is no fall in blood pressure during head-up tilt, unlike a subject with autonomic failure in whom blood pressure falls promptly and remains low with a blood pressure overshoot on return to the horizontal. In this subject there is only a minimal change in heart rate despite the marked blood pressure fall. In both subjects continuous blood pressure and heart rate was recorded with the Portapress II. (From Mathias 2006, with permission.)

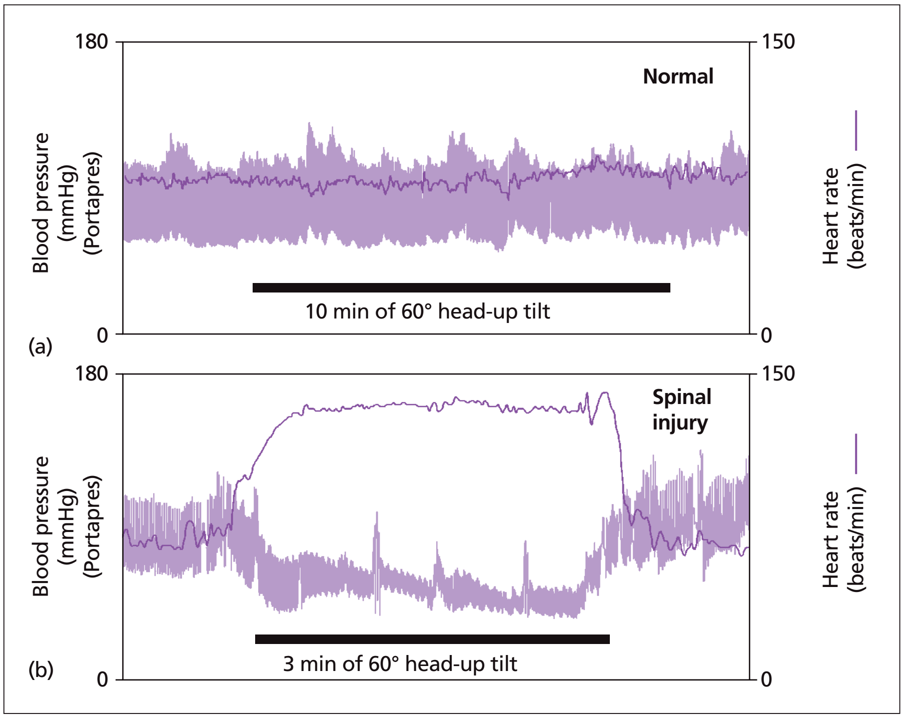


Figure 23.5 Blood pressure and heart rate measured continuously with the Portapres II in a patient with a high cervical spinal cord lesion. There is a fall in blood pressure because of impairment of the sympathetic outflow disrupted in the cervical spine. Heart rate rises because of withdrawal of vagal activity in response to the rise in pressure. (From Mathias 2006, with permission.)

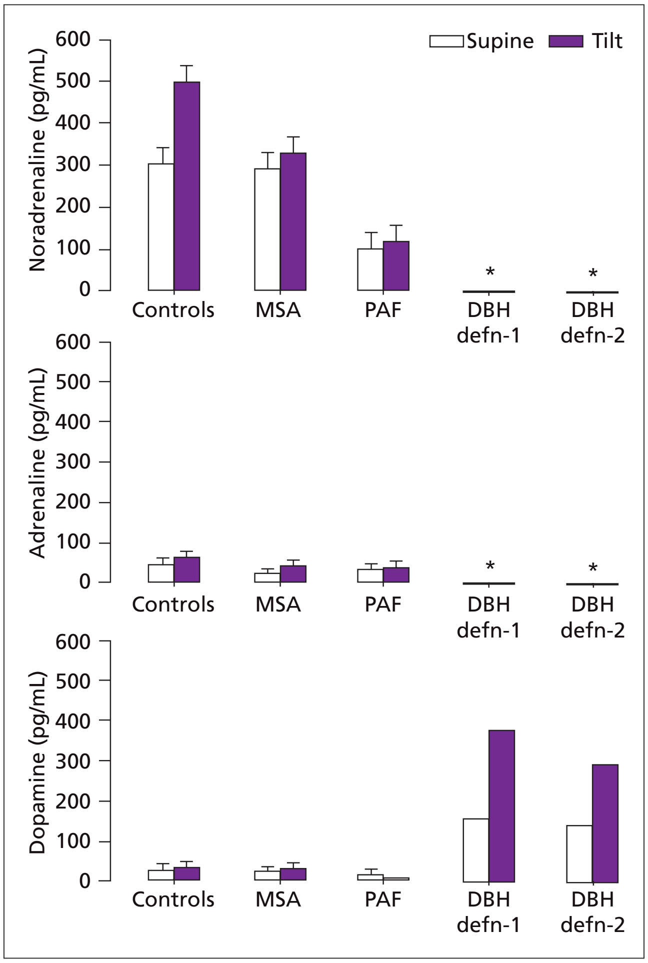


Figure 23.6 Plasma noradrenaline, adrenaline and dopamine levels (measured by high pressure liquid chromatography) in normal subjects (controls), patients with multiple system atrophy (MSA), pure autonomic failure (PAF) and two individual patients with dopamine β-hydroxylase (DBH) deficiency while supine and after head-up tilt to 45° for 10 minutes. The asterisk indicates levels below the detection limits for the assay, which are less than 5 pg/mL for noradrenaline and adrenaline and less than 20 pg/mL for dopamine. Bars indicate ± standard error of mean (SEM). (From Mathias & Bannister 1999, with permission.)

Table 23.6 Symptoms resulting from orthostatic hypotension and impaired perfusion.

Cerebral hypoperfusion
Dizziness
Visual disturbances
  Blurred – tunnel
  Scotoma
  Greying out – blacking out
  Colour defects
Syncope
Cognitive deficits

Muscle hypoperfusion
Paracervical and suboccipital ('coat-hanger') ache
Lower back/buttock ache

Subclavian steal-like syndrome

Renal hypoperfusion
Oliguria

Spinal cord hypoperfusion

Non-specific
Weakness, lethargy, fatigue
Falls

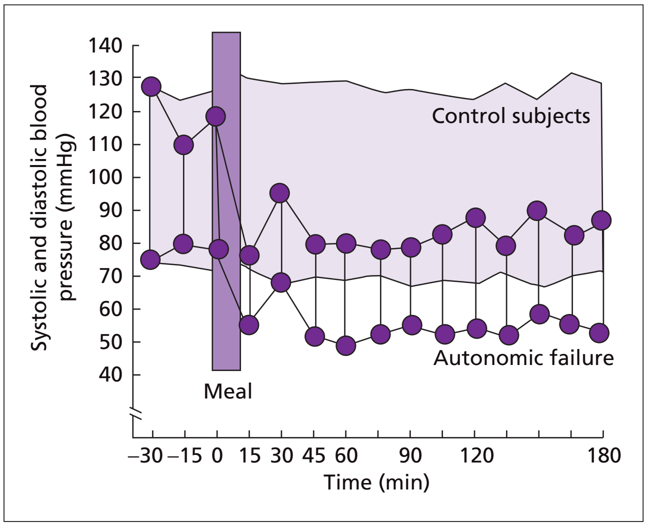


Figure 23.7 Changes in blood pressure (BP) before and after a standard meal in a group of normal subjects (stippled area) and in a patient with autonomic failure (IR), while in the supine and horizontal position. Bars indicate ± standard error of mean (SEM). In the normal subjects there is no change in BP. In the patient with autonomic failure there is a marked fall in BP soon after food ingestion, with levels falling to around 80/50 mmHg and remaining low for 3 hours, even in the supine position. (From Mathias & Bannister 2002, with permission.)

pressure recovers. The pain probably is caused by reduced perfusion of neck muscles that need to be tonically active to maintain upright head posture. Using arm muscles especially when upright can increase cerebral symptoms of orthostatic hypotension by a subclavian steal-like mechanism further reducing brainstem blood flow. Central chest pain, suggestive of angina pectoris, can occur with normal coronary arteries and may be caused by chest wall ischaemia.

Oliguria, especially during the day when upright, is the result of reduced renal perfusion pressure. This may be difficult to separate from retention of urine resulting from urinary sphincter abnormalities, e.g. in high spinal cord lesions. The reverse – polyuria – occurs when supine, especially at night when blood pressure is restored or even elevated.

In the elderly, falls may occur even without other symptoms of orthostatic hypotension. Other less specific symptoms include weakness, tiredness and fatigue.

A key component in the history is the relationship between symptoms and head-up postural change. Symptoms may be more prominent with rapid head-up change, e.g. getting out of bed in the morning and on rising after a large meal, excessive alcohol or exercise (Figures 23.7 and 23.8). A variety of factors influence orthostatic hypotension and should be sought in the history (Table 23.7).

Many patients recognize the association with head-up postural change and either sit down, lie flat, stoop or assume curious postures, such as squatting. These positions prevent the fall in blood pressure or even may elevate blood pressure. Orthostatic hypotension often is worsened by drugs that have vasodilator effects and are used to treat associated disease (levodopa or insulin), alleviate symptoms (nitrates) or reverse organ failure (sildenafil).

Syncope without orthostatic hypotension

Syncope has many causes (autonomic, cardiac, neurogenic and metabolic). Autonomic causes of syncope without orthostatic hypotension include neurally mediated syncope, where there is transient hypotension and bradycardia. There are three major forms: vasovagal syncope, carotid sinus hypersensitivity and situational syncope. Blood pressure falls because of sympathetic withdrawal while heart rate falls because of increased vagal activity. This is more likely to occur when upright. Between attacks usually there are no autonomic abnormalities. The history of the syncopal attack and its recovery often separates neurally mediated syncope from other neurological diseases, such as epilepsy. Recovery on lying flat usually is rapid, as this restores blood pressure and cerebral perfusion. Tongue biting normally does not occur. In some, convulsions result from hypoxia, especially if the subject is not laid flat and blood pressure recovery is delayed. Urinary incontinence may occasionally occur.

In vasovagal syncope (common faints or emotional syncope) provoking factors include fear, pain, the sight of blood and medical procedures, especially involving needles. Nausea and other gastrointestinal upsets, probably through activation of visceral afferents, may be causative. Palpitations and sweating may occur in the pre-syncopal phase. In those with an adequate

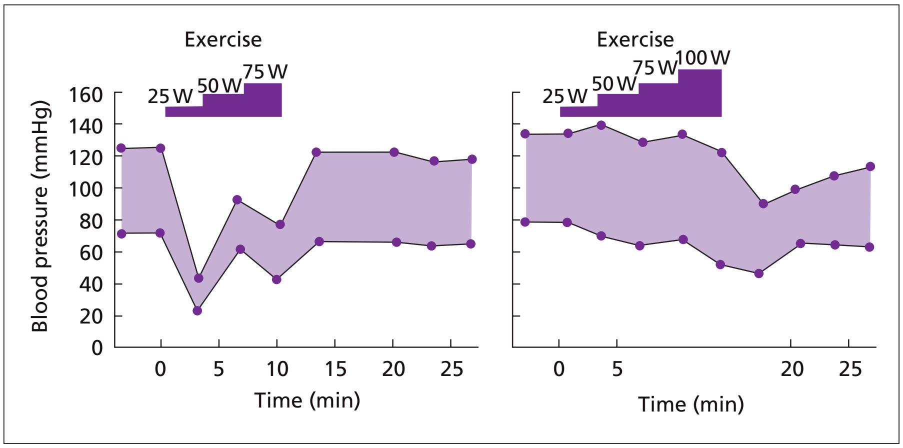


Figure 23.8 Systolic and diastolic blood pressure in two patients with autonomic failure before, during and after bicycle exercise performed with the patient in the supine position at different workloads, ranging from 25 to 100 W. In the patient on the left there is a marked fall in blood pressure on initiating exercise; she had to crawl upstairs because of severe exercise-induced hypotension. In the patient on the right, there are minor changes in blood pressure during exercise, but a marked decrease soon after stopping exercise. This patient was usually asymptomatic while walking, but developed postural symptoms when he stopped walking and stood still. It is likely that the decrease in blood pressure post-exercise was a result of vasodilatation in exercising skeletal muscle, not opposed by the calf muscle pump. (From Mathias & Williams 1994, with permission.)

Table 23.7 Factors influencing orthostatic hypotension.

Speed of positional change
Time of day (worse in the morning)
Prolonged recumbency
Warm environment (hot weather, central heating, hot bath)
Raising intrathoracic pressure – micturition, defaecation or coughing
Food and alcohol ingestion
Water ingestion*
Physical exertion
Physical manoeuvres and positions (bending forward, abdominal compression, leg crossing, squatting, activating calf muscle pump)†
Drugs with vasoactive properties (including dopaminergic agents)

* This raises blood pressure in autonomic failure.
† These manoeuvres usually reduce the postural fall in blood pressure, unlike the others.

warning, sitting or lying flat prevents syncope. The reverse, prolonged standing or assumption of the upright position on a tilt table, may provoke a response. The latter is the basis for the laboratory investigation. Tilt table testing usually is for 10 minutes, with a provocative stimulus such as venepuncture; sometimes prolonged tilt testing for 45 minutes is needed. It is important to determine the underlying mechanism contributing to syncope as this influences the management of vasovagal syncope (Figures 23.9–23.11).

In the elderly, carotid sinus hypersensitivity is increasingly recognized as a cause of falls (Figure 23.12). There may be a classic history of syncope induced while shaving, turning the head or buttoning the collar, when carotid afferents are stimulated. However, this history may not be obtained. Falls and syncope of unknown aetiology should arouse suspicion of this disorder.

In situational syncope, various factors predispose the individual to syncope. These include induction of a Valsalva manoeuvre and hyperventilation. This occurs in weight-lifters, trumpet-blowers, in mess tricks (deliberate manoeuvres) and following paroxysms of coughing. In micturition syncope, hypotension results probably from a combination of vasodilatation caused by warmth and/or alcohol and straining during micturition (which raises intrathoracic pressure and induces a Valsalva manoeuvre), compounded by release of the pressor stimulus arising from a distended bladder while standing upright. Swallowing-induced syncope may occur with glossopharyngeal neuralgia.

Orthostatic intolerance with posturally induced tachycardia

When orthostatic intolerance occurs without orthostatic hypotension, but with a substantial rise in heart rate (of over 30 beats/minute), the term 'postural tachycardia syndrome' (PoTS) is used (Figure 23.13). It predominantly affects women below the age of 50 years. Symptoms include marked dizziness on postural change or modest exertion; syncope may occur. There usually are no features of generalized autonomic failure. Associated disorders include the joint hypermobility syndrome (Ehlers–Danlos III; Figures 23.14 and 23.15), chronic fatigue syndrome, mitral valve prolapse and hyperventilation. A relationship to disorders described in wartime, such as da Costa's syndrome and soldier's heart, when dizziness and syncope on effort is accompanied by exhaustion, dyspnoea, headache, palpitations, and pain over the heart seems probable.

Hypertension

Unlike hypotension, hypertension typically causes few symptoms other than headaches – and these only occasionally.

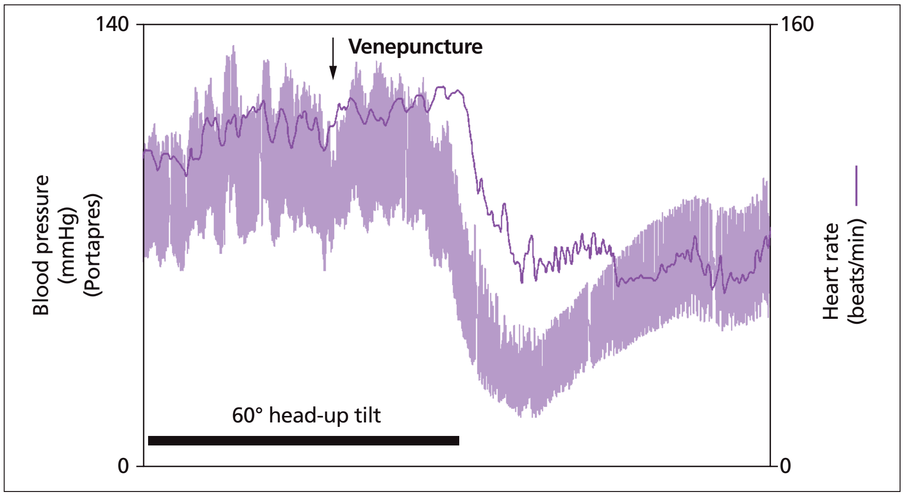


Figure 23.9 Blood pressure and heart rate with continuous recordings from the Portapres II in a patient with the mixed (cardio-inhibitory and vasodepressor) form of vasovagal syncope. (From Mathias 2006, with permission.)

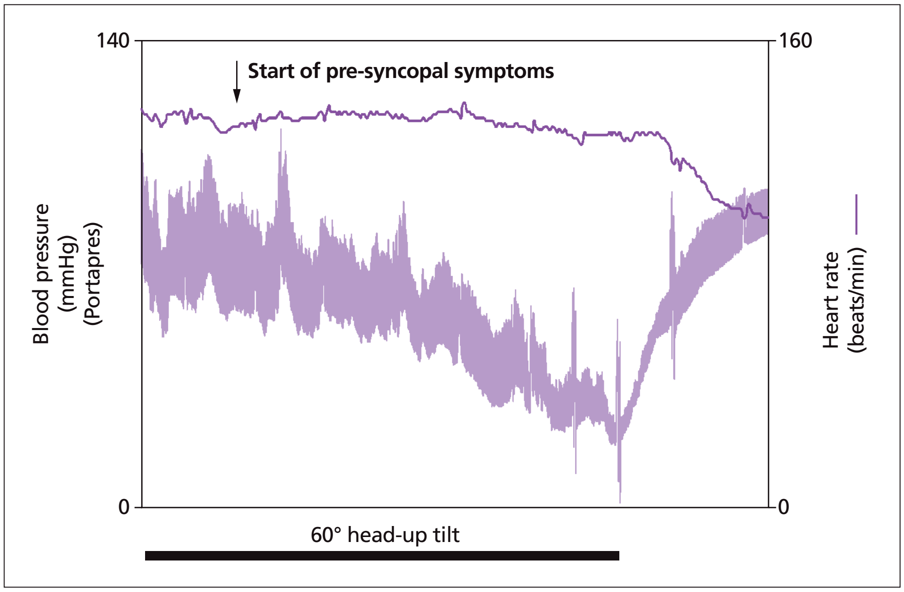


Figure 23.10 Blood pressure and heart rate with continuous recordings from the Portapres II in a patient with the predominantly vasodepressor form of vasovagal syncope.

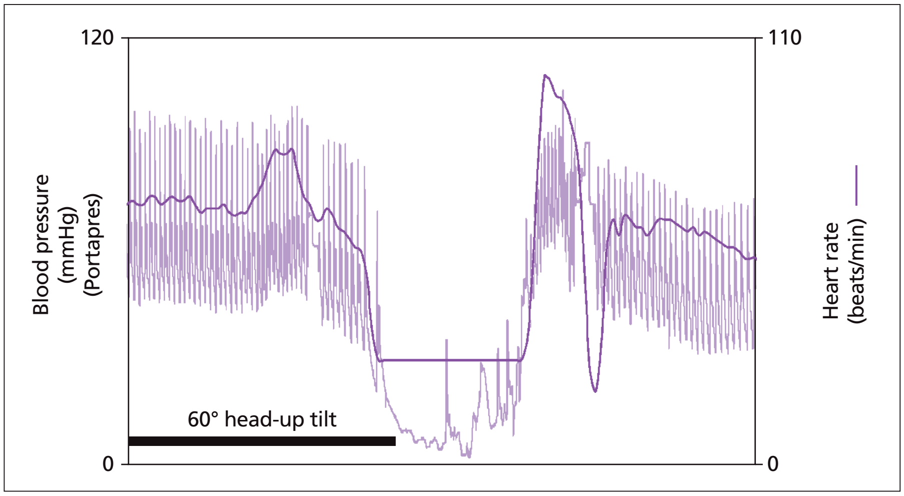


Figure 23.11 Blood pressure and heart rate with continuous recordings from the Portapres II in a patient with the cardio-inhibitory form of vasovagal syncope.

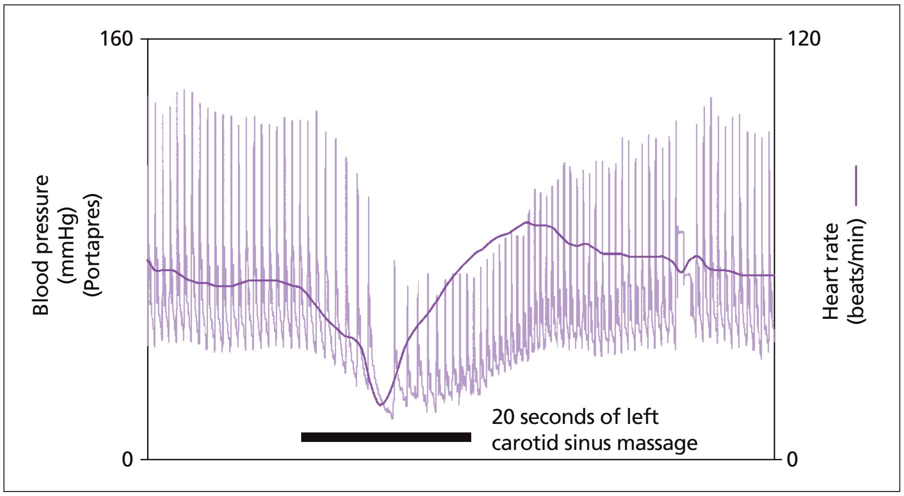


Figure 23.12 Continuous blood pressure and heart rate measured non-invasively (by Portapres) in a patient with falls of unknown aetiology. Left carotid sinus massage caused a fall in both heart rate and blood pressure. The findings indicate the mixed (cardio-inhibitory and vasodepressor) form of carotid sinus hypersensitivity. (From Mathias & Bannister 2002, with permission.)

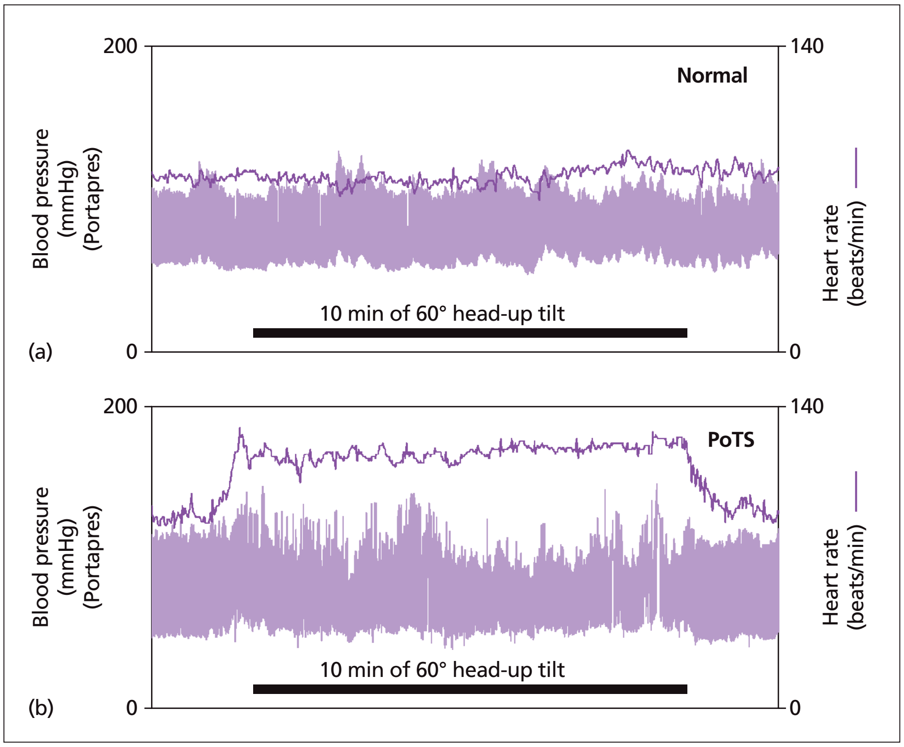
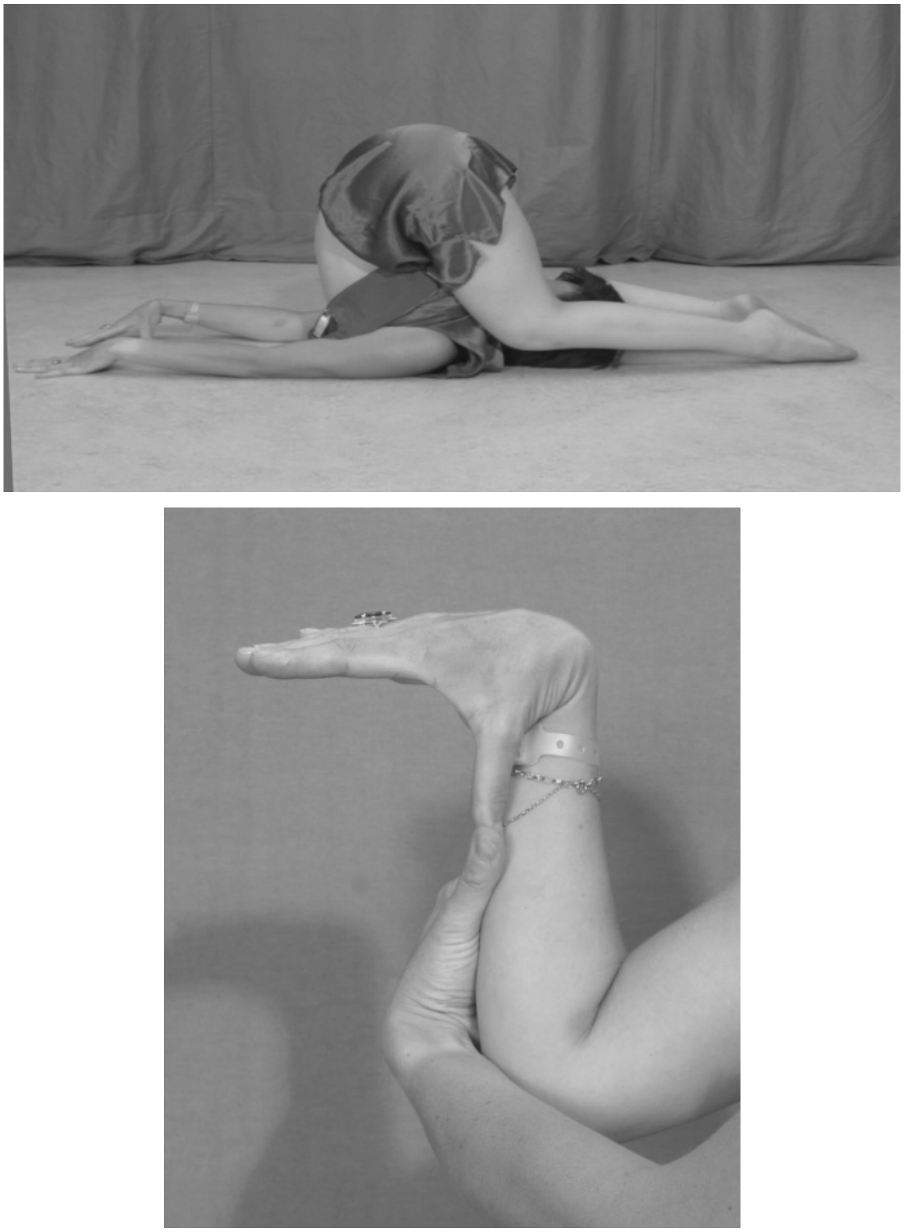


Figure 23.13 Blood pressure and heart rate measured continuously before, during and after 60° head-up tilt by the Portapres II in (a) a normal subject, and (b) in subject with the postural tachycardia syndrome (PoTS). (From Mathias 2002, with permission.)

- In high spinal cord lesions, severe paroxysmal hypertension can develop as part of autonomic dysreflexia, when an uninhibited increase in spinal sympathetic activity is caused by contraction of the urinary bladder, irritation of the large bowel, noxious cutaneous stimulation or skeletal muscle spasms. This can cause hypertension, a throbbing pounding headache, palpitations with bradycardia and sweating/flushing over the face and neck. The limbs tend to be cold as a result of peripheral vasoconstriction.
- In tetanus, hypertension in ventilated patients may be precipitated by muscle spasms or tracheal suction.
- Intermittent hypertension may occur in the Guillain–Barré syndrome, porphyria, posterior fossa tumours and phaeochromocytoma (Figure 23.16), often without any evident precipitating cause.
- Sustained hypertension resulting from increased sympathetic activity may occur in subarachnoid haemorrhage.
- Hypertension in the supine position may complicate orthostatic hypotension in pure autonomic failure (PAF). The mechanisms include impaired baroreflex activity, adrenoceptor supersensitivity, an increase in central blood volume because of



Figures 23.14 and 23.15 Joint hyperextensibility as demonstrated by a subject with the joint hypermobility syndrome and postural tachycardia syndrome (PoTS).

a shift from the periphery and the effects of drugs used to prevent orthostatic hypotension.

Heart rate disturbances

Bradycardia, along with hypertension, may occur in cerebral tumours with or without raised intracranial pressure and during autonomic dysreflexia in high spinal cord injuries. In the latter, the afferent and vagal efferent components of the baroreflex arc are intact, and the heart slows in an attempt to control the rise in blood pressure. In phaeochromocytoma, bradycardia with escape rhythms and atrioventricular dissociation may occur in response to a rapid rise in blood pressure.

Severe bradycardia can occur in artificially ventilated high cervical cord injuries with diaphragmatic paralysis. Their intact vagi are sensitive to hypoxia. Stimuli such as tracheal suction can readily induce bradycardia and even cardiac arrest. The inability to increase sympathetic activity is likely to contribute. Similar responses also may occur in tetraplegic patients during general anaesthesia, especially when muscle paralysis followed by intubation is performed without atropine.

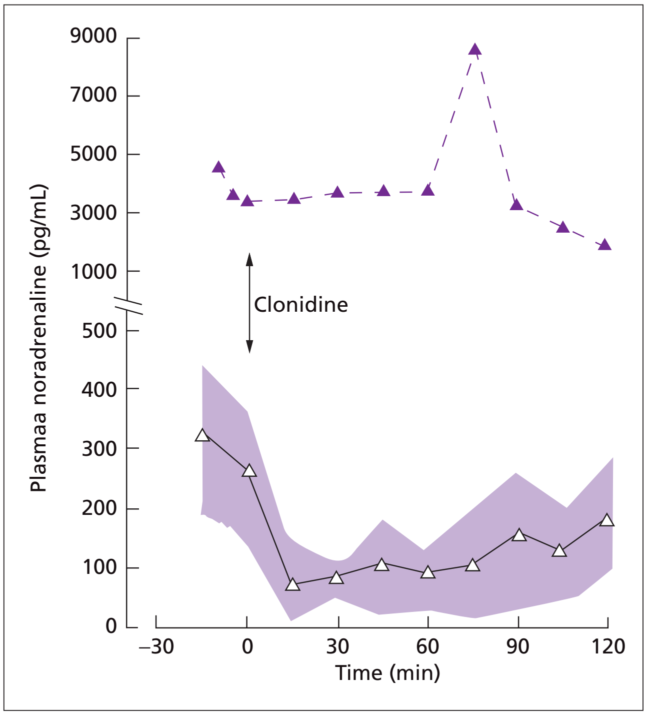


Figure 23.16 Plasma noradrenaline levels in a patient with a phaeochromocytoma (black triangles) and in a group of patients with essential hypertension (open triangles) before and after intravenous clonidine, indicated by an arrow (2 μg/kg over 10 minutes). Plasma noradrenaline levels fall rapidly in the essential hypertensives after clonidine and remain low over the period of observation. The stippled area indicates the +/– standard error of mean (SEM). Plasma noradrenaline levels are considerably higher in the phaeochromocytoma patient and are not affected by clonidine. (From Mathias & Bannister 2002, with permission.)

In neurally mediated syncope, severe bradycardia may occur in conjunction with hypotension. Syncope can even occur when the heart rate is preserved by a cardiac demand pacemaker, because sympathetic withdrawal alone can cause substantial vasodilatation resulting in hypotension.

In diabetes mellitus, the presence of a cardiac vagal neuropathy may result in higher resting heart rate and impaired sinus arrhythmia and other tests of cardiac parasympathetic function (Figure 23.17). Disorders of cardiac conduction are common in Chagas disease (South American trypanosomiasis) and may occur in amyloidosis.

In PoTS, tachycardia usually is associated with head-up postural change and exertion. Tachycardia resulting from increased sympathetic discharge may occur along with hypertension in the Guillaine–Barré syndrome and in tetanus. In phaeochromocytoma, tachycardia results from catecholamine release and β-adrenoceptor stimulation.

Facial and peripheral vascular changes

When blood pressure falls in postural hypotension or neurally mediated syncope, there is usually facial pallor with an ashen appearance. Restoration of colour follows promptly on assuming the supine position when blood pressure rises. Facial pallor also may occur during an attack in phaeochromocytoma but usually is accompanied by sweating, headache and hypertension. In long-standing tetraplegia, hypertension during autonomic dysreflexia is often accompanied by flushing and sweating over the face and neck. The precise mechanisms are unknown.

In Harlequin syndrome (see below) there is vasodilatation and anhidrosis on one side of the face caused by sympathetic

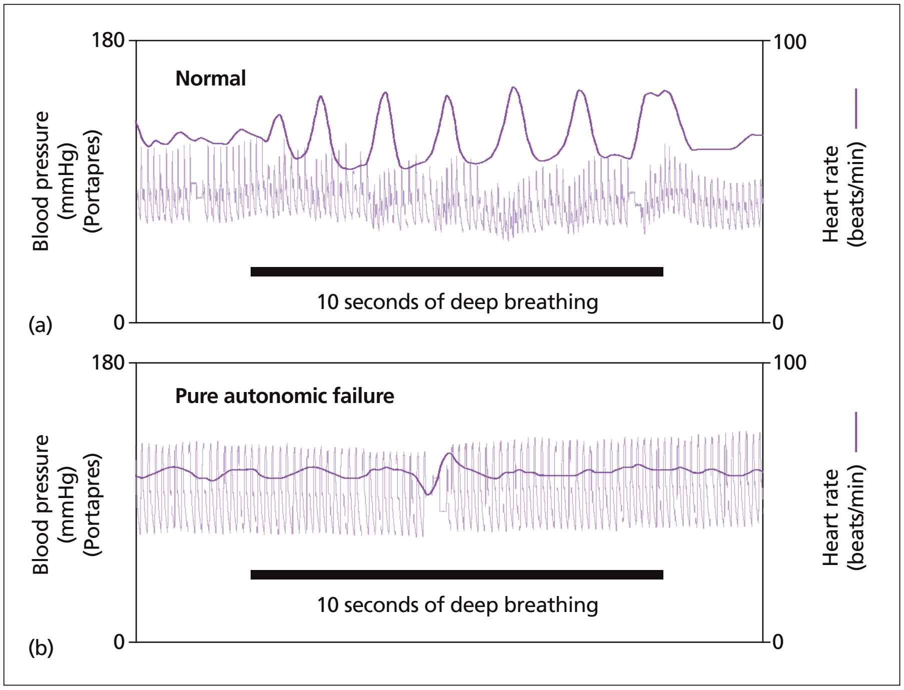


Figure 23.17 (a) Rise and fall in heart rate (sinus arrhythmia) in a normal subject. (b) These responses are diminished in autonomic failure affecting the cardiac parasympathetic.

impairment, with sparing of the pupil. The lesion spares the first thoracic segment (from which oculomotor fibres often leave) but affects sympathetic fibres of the second and third thoracic roots.

Raynaud's phenomenon may be seen in both PAF and MSA, for uncertain reasons. In the latter, cold purplish blue hands and feet can be particularly troublesome. Livedo reticularis can accompany sympathetic over-activity, as in phaeochromocytoma. In erythromelalgia (Chapter 22) there is limb discomfort with vascular changes. The precise reasons for the cutaneous, vascular and sudomotor changes in reflex sympathetic dystrophy (chronic region pain disorder), remain debatable.

Sudomotor system

The eccrine glands concerned with temperature regulation are innervated by sympathetic cholinergic fibres, unlike apocrine glands on palms and soles which are influenced by circulating substances, including catecholamines. Anhidrosis or hypohidrosis is common in PAF and differences in sweating may first be noticed during exposure to warm temperatures. Occasionally, hyperhidrosis in segmental areas may be a disconcerting symptom, as a compensatory response to diminished sudomotor activity elsewhere. Anhidrosis may be congenital and occur without any other deficit. It may be an integral component of certain hereditary sensory and autonomic neuropathies, such as congenital insensitivity to pain with anhidrosis (HSAN Type IV; Chapter 22).

Localized or generalized anhidrosis, sometimes with compensatory hyperhidrosis, may be associated with the Holmes–Adie pupil (Plates 23.1–23.3). This association is known as Ross's syndrome. In spinal cord injuries, there often is a band of hyperhidrosis above the lesion with anhidrosis below. During autonomic dysreflexia in high spinal lesions sweating occurs mainly over the face and neck. Facial and truncal hyperhidrosis may occur in Parkinson's disease. Hyperhidrosis is seen intermittently in phaeochromocytoma and accompany hypertension in tetanus.

Localized hyperhidrosis over the face and neck caused by food (gustatory sweating) can be socially distressing. It occurs in diabetes mellitus, following Bell's palsy and after parotid surgery, as a result of aberrant connections between nerve fibres supplying the salivary and sweat glands. Minimally invasive endoscopic techniques for sympathectomy often are successful in reducing axillary and palmar hyperhidrosis, but some develop troublesome compensatory hyperhidrosis over innervated areas of the trunk and lower limbs. The mechanisms are unclear.

Hypothermia can occur in hypothalamic disorders and in the elderly, in whom degenerative hypothalamic lesions are sometimes postulated. In high spinal injuries, especially in the early phases, the absence of 'shivering thermogenesis' and inability to vasoconstrict and thus prevent heat loss can readily result in hypothermia. Hypothermia may be missed if oral temperature only is recorded without a low-reading thermometer. Measurement of core tympanic or rectal temperature is essential.

Hyperpyrexia may be a problem with anhidrosis, with exposure to high ambient temperatures. Heat also increases vasodilatation and can enhance orthostatic hypotension leading to collapse.

Alimentary system

Reduced salivation and a dry mouth (xerostomia) occur in autonomic disease, especially in pure cholinergic dysautonomia. It may cause dysphagia, prominent when eating dry food. The lower two-thirds of the oesophagus contains smooth muscle innervated autonomically. Diseases affecting these pathways often cause dysphagia. Dysphagia is unusual in PAF, but often occurs in the later stages of MSA, where the problem often is in the oropharyngeal region and may result in tracheal aspiration. The oesophagus often is involved in Chagas disease, with achalasia and mega-oesophagus causing vomiting. Gastric stasis in diabetes mellitus may cause abdominal distension and vomiting of undigested food.

Constipation is common in PAF. Diarrhoea also may occur as result of overflow. Diarrhoea, especially at night, can be a distressing problem in diabetes mellitus. Reasons postulated include incomplete digestion, altered bowel flora and abnormal motility, but the cause remains poorly understood.

Kidneys and urinary tract

Nocturnal polyuria is a frequent symptom in PAF. The causes include restitution of blood pressure sometimes to elevated levels while supine, redistribution of blood from the peripheral into the central compartment, and alteration in release of hormones that influence salt and water handling (such as renin, aldosterone and atrial natriuretic peptide). In MSA, where there is additional autonomic impairment of bladder and sphincter control, nocturia can be particularly troublesome. By day, the low level of blood pressure when upright is likely to cause oliguria.

Autonomic disease can cause urinary frequency, urgency, incontinence or retention. Loss of sacral parasympathetic function, as in the early phase of spinal cord injury, causes an atonic bladder with urinary retention, whereas recovery of isolated spinal cord function results in a neurogenic bladder. Dyssynergia, with detrusor contraction but without sphincter relaxation, causes autonomic dysreflexia. Ureteric reflux predisposes to renal damage, especially in the presence of infection. In PAF, urinary symptoms initially may be attributed in older men to prostatic hypertrophy and in women to pelvic muscle weakness, especially in those who are multiparous. In MSA, surgery in suspected prostate enlargement usually is of no benefit. The use of drugs with anticholinergic effects may unmask urinary bladder dysfunction in autonomic failure.

Infection is common when bladder dysfunction causes urinary stasis. Some, such as those with spinal injuries, are prone to urinary calculi, especially when immobility increases calcium excretion.

Sexual function

In the male, failure of erection, dependent partly on the parasympathetic system, may cause impotence. Ejaculation is controlled by the sympathetic system. Retrograde ejaculation may occur, especially if there are urinary sphincter abnormalities. Dissociating the effects of increasing age, systemic illness and depression from definable organic causes of impotence may be difficult. The effect of drug therapy needs consideration. The 5-HT uptake inhibitor, fluoxetine, prolongs ejaculation. Others normally not considered to have autonomic side effects, such as thiazides used in hypertension, may diminish sexual potency.

Priapism resulting from abnormal spinal reflexes may occur in patients with spinal cord lesions. In women, autonomic impairment does not appear directly to affect sexual function, although this has been inadequately studied.

Eyes and lacrimal glands

The non-striated component of the levator palpebrae superioris (Müller's muscle) is innervated by sympathetic fibres. Mild ptosis is part of Horner's syndrome. If sympathetic lesions are bilateral, as in high spinal cord transection, Horner's syndrome is difficult to detect. A variety of pupillary abnormalities may occur with autonomic involvement, miosis in Horner's syndrome and dilated myotonic pupils in Holmes–Adie syndrome (Plates 23.2 and 23.3). Symptoms directly relating to ocular function may be minimal in such disorders. Night vision is impaired in sympathetic denervation. There is reduced tolerance to sunlight when pupils are dilated following parasympathetic failure. The ciliary muscle is innervated by parasympathetic nerves: blurred vision caused by cycloplegia may follow disease or anticholinergic drugs. The latter also may raise intra-ocular pressure and cause glaucoma.

Impaired tear production may occur in PAF, sometimes as part of a presumed sicca or Sjögren's syndrome, along with diminished salivary secretion. Excessive and inappropriate lacrimation occurs in crocodile tears syndrome (gusto-lacrimal reflex).

Respiratory system

Involuntary inspiratory sighs, stridor and snoring of recent onset are more frequent in MSA than in Parkinson's disease. Stridor results from weakness of the crico-arytenoid muscles, the main laryngeal abductors. Nocturnal apnoea, which occurs in the later stages of the disorder, is caused by involvement of brainstem respiratory centres.

Abnormal responses following activation of reflexes from the respiratory tract, such as during tracheal suction, may cause profound cardiovascular disturbances. The following occur:

- In tetanus, severe hypertension and tachycardia;
- In high cervical cord transaction, bradycardia and cardiac arrest.

Additional features of neurological conditions: MSA and Parkinson's disease

In the parkinsonian form of MSA, bradykinesia and rigidity with minimal tremor are more likely than in idiopathic Parkinson's disease (Figure 23.18). This causes difficulties in mobility, especially turning in bed and changing direction. Facial expression is affected to a lesser degree in MSA than in idiopathic Parkinson's disease. In MSA there often is a response to antiparkinsonian agents in the early stages. Drug side effects, such as orthostatic hypotension, are likely to occur as the disease progresses. In Parkinson's disease with autonomic failure, extrapyramidal features often have been present for a long period and usually remain responsive to levodopa therapy.

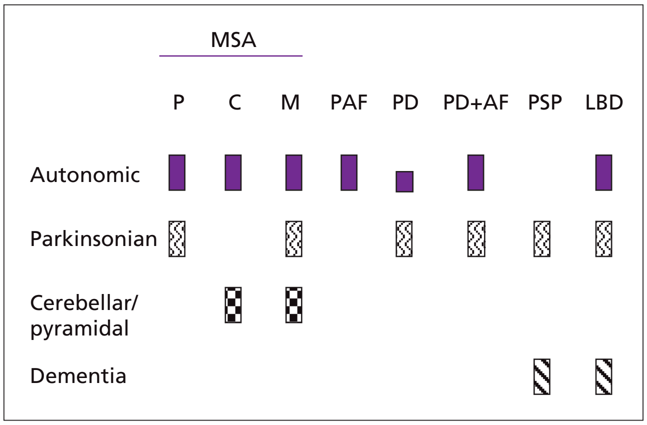


Figure 23.18 The major clinical features in parkinsonian syndromes and allied disorders with autonomic failure. These include the three major neurological forms of multiple system atrophy (MSA); the parkinsonian form (MSA-P, also called striatonigral degeneration), the cerebellar form (MSA-C, also called olivopontocerebellar atrophy) and the multiple or mixed form (MSA-M, which has features of both other forms), pure autonomic failure (PAF), idiopathic Parkinson's disease (IPD), Parkinson's disease with autonomic failure (PD + AF), progressive supranuclear palsy (PSP) and diffuse Lewy body disease (LBD). After Mathias (1997, 2005).

In the non-parkinsonian forms of MSA, cerebellar features predominate with an ataxic gait, intention tremor, scanning speech and nystagmus. Ataxia may be difficult to separate from or may be compounded by unsteadiness caused by orthostatic hypotension. There also may be pyramidal involvement with increased tone, exaggerated tendon reflexes and extensor plantar responses.

In the mixed form of MSA, a varying combination of extrapyramidal, cerebellar and pyramidal features is seen. Sensory deficits are uncommon in MSA.

Patients with secondary autonomic failure have neurological features that are a part of, or a complication of, a primary disease. In diabetes mellitus, a sensorimotor neuropathy often coexists with, or precedes the autonomic neuropathy.

Psychological and psychiatric disturbances

Dementia is unusual in PAF. Most patients with MSA are not clinically depressed, despite their disabilities and the probable deficit in central catecholamine levels. Overall, they tend to have a normal affective state, especially when comparisons are made with Parkinson's disease. In PAF there is no psychological disorder, but the absent autonomic responses may result in subtle emotional deficits. They appear less emotional than normal subjects and, when compared with similarly disabled patients with Parkinson's disease without autonomic failure, are less anxious. Cognitive function may transiently be affected when blood pressure falls below critical cerebral perfusion pressure limits. Whether this affects certain tasks, e.g. involving attention, rather than others, is unclear.

Anxiety and tremulousness may occur in phaeochromocytoma. Psychological factors may contribute to vasovagal syncope (hence the term 'emotional syncope') and also in essential hyperhidrosis. Whether this is the cause, or result, of the autonomic condition can be difficult to dissect. Psychiatric disturbances may also complicate conditions such as porphyria.

Clinical examination

A detailed physical examination is essential and, with the symptoms elicited, may provide important clinical pointers towards autonomic disease. Features on general examination include dryness of skin, hyperhidrosis or cold hands in Raynaud's disease, and pupillary changes. Measurement of blood pressure, both lying and standing (or sitting), is needed to determine if orthostatic hypotension is present, as is recording the pulse rate changes in patients with PoTS. The extent and distribution of the neurological abnormalities provide important clues to underlying central or peripheral autonomic disorders. Examination of other systems, as in hepatic disease or diabetes, is necessary along with urine testing for glucose and protein.

The combination of a detailed history and physical examination is crucial in determining if autonomic disease is present, in ascertaining the probable underlying diagnosis, and also for interpreting the results of autonomic tests in the context of the associated disorder.

Investigations

The aims of investigations in autonomic dysfunction are twofold. The first relates to diagnosis. The second is to understand the pathophysiological basis of disturbed autonomic function, as this often forms the basis of treatment strategies and their evaluation. An outline is provided in Table 23.8. Details of the tests are provided elsewhere.

Management

The management of autonomic dysfunction encompasses a number of aspects. Of immediate and practical importance is alleviation of symptoms. The ideal is to rectify the autonomic deficit and cure the underlying disorder but this rarely is achieved. Autonomic disease often involves various systems. Basic principles in relation to management of the major clinical features are provided here. Specific aspects will vary in different diseases and always should be directed to the needs of the individual patient.

Table 23.8 Outline of investigations in autonomic disease.

Cardiovascular

Physiological

Head-up tilt (60°);* standing;* Valsalva maneouvre*
Pressor stimuli* (isometric exercise, cold pressor, mental arithmetic)
Heart rate responses – deep breathing,* hyperventilation,* standing,* head-up tilt,* 30 : 15 R–R interval ratio
Liquid meal challenge
Exercise testing
Carotid sinus massage

Biochemical

Plasma noradrenaline: supine and head-up tilt or standing; urinary catecholamines; plasma renin activity and aldosterone

Pharmacological

Noradrenaline: alpha-adrenoceptors, vascular
Isoprenaline: beta-adrenoceptors, vascular and cardiac
Tyramine: pressor and noradrenaline response
Edrophonium: noradrenaline response
Atropine: parasympathetic cardiac blockade

Imaging

Cardiac sympathetic innervation with MIBG or fluoro-dopamine

Endocrine

Clonidine – alpha-2 adrenoceptor agonist: noradrenaline suppression; growth hormone stimulation

Sudomotor

Central regulation thermoregulatory sweat test
Sweat gland response to intradermal acetylcholine, quantitative sudomotor axon reflex test, localized sweat test
Sympathetic skin response

Gastrointestinal

Video-cine-fluoroscopy, barium studies, endoscopy, gastric emptying studies, lower gut studies

Renal function and urinary tract

Day and night urine volumes and sodium/potassium excretion
Urodynamic studies, intravenous urography, ultrasound examination, sphincter electromyography

Sexual function

Penile plethysmography
Intracavernosal papaverine

Respiratory

Laryngoscopy
Sleep studies to assess apnoea and oxygen desaturation

Eye and lacrimal function

Pupil function, pharmacological and physiological
Schirmer's test

* Screening tests widely used.

Cardiovascular system

Orthostatic hypotension

Orthostatic hypotension may cause few symptoms in some but can cause considerable distress in others. It may contribute to disability and even death because of the potential risk of substantial injury. Treatment may be needed even in those who are asymptomatic, as they are at risk in situations such as fluid depletion or treatment with vasodilator drugs when there may be marked falls in blood pressure.

No single drug or treatment can effectively replace the actions of the sympathetic nervous system in different situations. A multi-pronged approach, combining non-pharmacological and pharmacological measures, is usually needed (Table 23.9).

The doctor and patient should be aware of the limitations of treatment. Furthermore, associated deficits (such as cerebellar features in MSA) may limit mobility in some, despite effective treatment of orthostatic hypotension.

Increasing patient awareness of factors that lower blood pressure is important. Rapid postural change, especially in the morning when getting out of bed, must be avoided because the supine blood pressure often is lowest at this time. Prolonged bed rest and recumbency through factors that include decompensation may contribute to orthostatic intolerance even in healthy individuals and can considerably worsen orthostatic hypotension in autonomic failure. Head-up tilt at night is beneficial and may reduce salt and water loss by stimulating the renin–angiotensin–aldosterone system. Straining during micturition and defaecation lowers blood pressure further by inducing a Valsalva manoeuvre. In toilets in small enclosed areas, e.g. in aircraft, the severe hypotension induced can be dangerous because of the inability to fall to the floor and thereby recover blood pressure and consciousness. In hot weather, because of impairment of thermoregulatory mechanisms, the rise in body temperature will increase cutaneous vasodilatation and worsen orthostatic hypotension. Ingestion of alcohol or large meals, especially those with a high carbohydrate content, causes splanchnic vasodilatation and postprandial hypotension which can aggravate orthostatic hypotension. Various physical manoeuvres, such as leg crossing, squatting, sitting in the knee–chest position and abdominal compression, reduce orthostatic hypotension (Figure 23.19). Drugs needed for associated symptoms (such as dopaminergic drugs) or to improve quality of life (sildenafil for erectile failure) may lower blood pressure further.

Table 23.9 Approaches to management of orthostatic hypotension, e.g. in chronic autonomic failure.

Non-pharmacological measures
To be avoided
Sudden head-up postural change (especially on waking)
Prolonged recumbency
Straining during micturition and defaecation
High environmental temperature (including hot baths)
Severe exertion
Large meals (especially with refined carbohydrate)
Alcohol
Drugs with vasodepressor properties
To be introduced
Head-up tilt during sleep
Small frequent meals
High salt intake
Judicious exercise (including swimming)
Body positions and manoeuvres
To be considered
Elastic stockings
Abdominal binders
Water ingestion
Pharmacological measures
Starter drug (fludrocortisone)
Sympathomimetics (ephedrine, midodrine, L-DOPS)
Specific targeting (octreotide, desmopressin, erythropoietin)

L-DOPS, L-dehydroxyphenylserine

Lower limb elastic compression stockings, abdominal binders and positive-gravity suits reduce venous pooling during standing. Each has its limitations and may increase susceptibility to orthostatic hypotension when not in use. Water ingestion (250–500 mL) raises blood pressure substantially in PAF by mechanisms that remain unclear (Figures 23.20 and 23.21). The ensuing diuresis may be troublesome, especially in MSA with associated urinary bladder disturbances.

Drugs that act in a variety of ways to raise blood pressure often are needed in association with non-pharmacological measures in moderate to severe orthostatic hypotension (Table 23.10).

A valuable starter drug is fludrocortisone in 50–100 μg at night or twice daily. It acts by retaining salt and water and increasing the sensitivity of blood vessels to pressor substances. In some ankle oedema, and with higher doses hypokalaemia, are unwanted effects.

The second line of drugs include those that mimic actions of noradrenaline. They include ephedrine (15 mg t.d.s. to a maximum of 45 mg t.d.s.), which acts both directly and indirectly. It raises blood pressure in central and incomplete autonomic lesions, including MSA. In peripheral sympathetic lesions, such as PAF, it may have minimal effects. Tachycardia, tremor and insomnia may limit use of higher doses. In peripheral lesions, where ephedrine may not be effective, midodrine (2.5 μg to a maximum of 10 μg t.d.s) is used. It is converted to the active metabolite, desglymidodrine, which acts on α-adrenoceptors. Side effects include a tingling scalp, goose pimples and, in the male, urinary retention. The ergot alkaloid, dihydro-ergotamine, acts predominantly on venous capacitance vessels, but its effects are limited by its poor absorption necessitating high oral doses (5–10 mg t.d.s).

In dopamine beta-hydroxylase (DβH) deficiency, a rare genetic disorder, there is an absence of plasma noradrenaline and adrenaline with increased plasma dopamine levels, resulting in severe

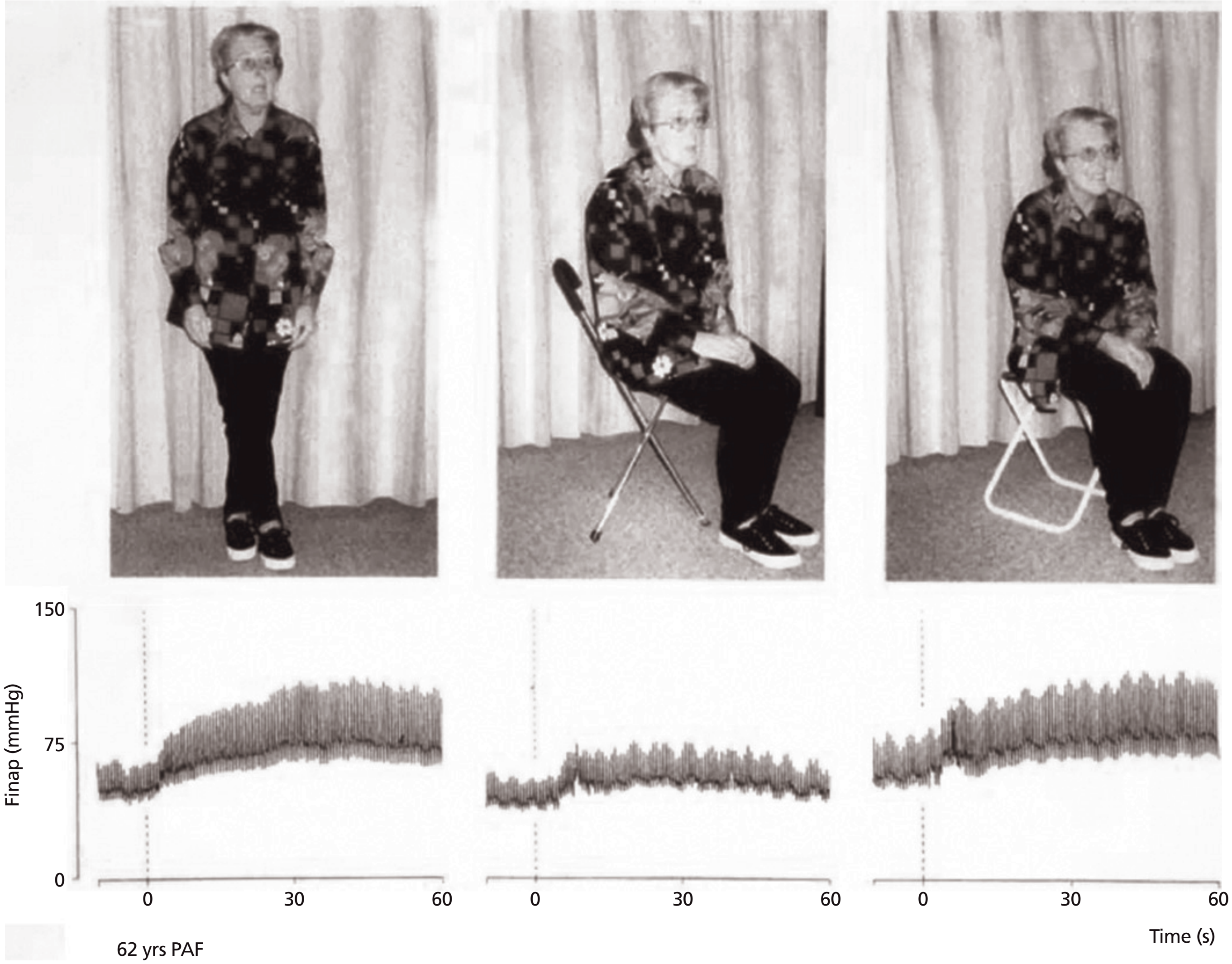


Figure 23.19 Physical counter-manoeuvres using isometric contractions of the lower limbs and abdominal compression. The effects of leg crossing in standing and sitting position, placing a foot on a chair and squatting on finger arterial blood pressure in a 54-year-old female subject with pure autonomic failure (PAF) and incapacitating postural hypotension. The subject was standing prior to the manoeuvres during which there is an increase in blood pressure and the pulse pressure. The effect on finger arterial blood pressure (Finap) of standing in the crossed leg position with leg muscle contraction (left), and sitting on a Derby chair (middle), or fishing chair (right) in a patient with autonomic failure and orthostatic hypotension. Orthostatic symptoms were present initially when standing and disappeared on crossing legs and sitting on the fishing chair. Sitting on the Derby chair caused the least rise in blood pressure and did not relieve completely the patient's symptoms. (From Smit AAJ, Hardjowijona MA, Wieling W. Are portable folding chairs useful to combat orthostatic hypotension? *Ann Neurol*; 1997, **42**; 975–978 with permission.)

orthostatic hypotension (Figure 23.22). Symptoms may be noted during infancy with hypotension, hypotonia and hypothermia. Children with DβH deficiency cannot exercise fully because their blood pressure falls, causing syncope. Symptoms usually worsen during the first two decades. Severe orthostatic hypotension becomes prominent in adulthood. DβH deficiency is caused by changes in *DBH* gene expression and inherited as an autosomal recessive disorder. Restoration of plasma noradrenaline is achieved by treatment with the precursor of noradrenaline, L-threo-3–4-dihydroxyphenylserine (DOPS), which has a structure similar to noradrenaline but with a carboxyl group. It can be given by mouth and is converted from the inert form to noradrenaline by the enzyme dopa decarboxylase, thus bypassing the Dβ-H deficiency. It thus replaces the deficient neurotransmitter and has been remarkably effective in this condition (Figure 23.23). DOPS may benefit other patient groups with PAF.

Specific targeting of pathophysiological mechanisms should be introduced when the combination of fludrocortisone and sympathomimetics is not effective. Nocturnal polyuria often worsens morning orthostatic hypotension. The vasopressin-2 receptor agonist, desmopressin, orally at night (e.g. 5–40 μg intranasally) is a potent antidiuretic with minimal direct pressor activity. In

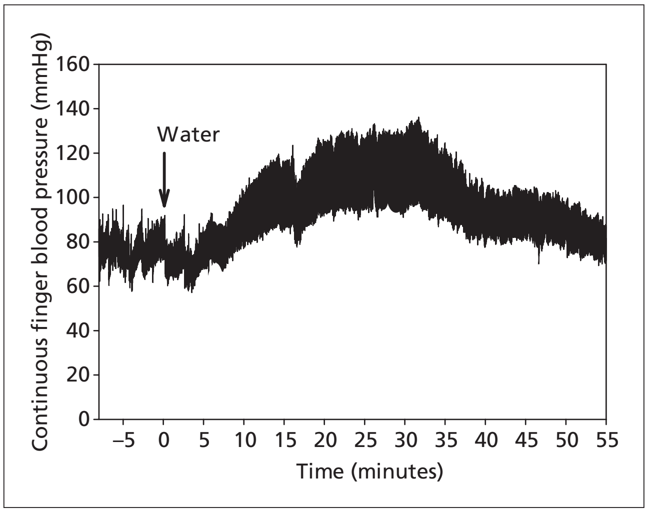


Figure 23.20 Changes in blood pressure before and after 500 mL distilled water ingested at time '0' in a patient with pure autonomic failure. Blood pressure is measured continuously using the Portapres II. (From Cariga & Mathias 2001, with permission.)

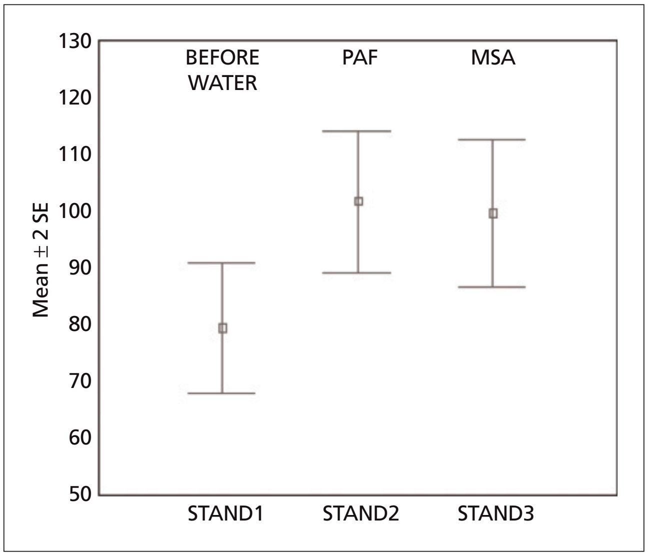


Figure 23.21 Standing blood pressure in seven pure autonomic failure (PAF) and seven multiple system atrophy (MSA) patients before and 15 and 30 minutes after ingestion of 500 mL water. (From Young & Mathias 2004, with permission.)

Table 23.10 Outline of mechanisms by which drugs may reduce postural hypotension.

Reducing salt loss/plasma volume expansion
Mineralocorticoids (fludrocortisone)

Reducing nocturnal polyuria
V_2-receptor agonists (desmopressin)

Vasoconstriction
Sympathetic
On resistance vessels (ephedrine, midodrine, phenylephrine, noradrenaline, clonidine, tyramine with monoamine oxidase inhibitors, yohimbine, L-dihydroxyphenylserine)
On capacitance vessels (dihydroergotamine)

Non-sympathomimetic
V_1-receptor agents (terlipressin)

Increasing acetylcholine
Acetylcholine esterase inhibitors (pyridostigmine)

Preventing vasodilatation
Prostaglandin synthetase inhibitors (indometacin, flurbiprofen)
Dopamine receptor blockade (metoclopramide, domperidone)
$Beta_2$-adrenoceptor blockade (propranolol)

Preventing postprandial hypotension
Adrenosine receptor blockade (caffeine)
Peptide release inhibitors (somatostatin analogue: octreotide)

Increasing cardiac output
Beta-blockers with intrinsic sympathomimetic activity (pindolol, xamoterol)
Dopamine agonists (ibopamine)

Increasing red cell mass
Erythropoietin

MSA with nocturia also caused by bladder disturbances, desmopresssin may be of considerable benefit in allowing less disturbed rest. Smaller doses are needed in PAF patients who appear more sensitive than those with MSA. Plasma sodium should be measured at intervals to exclude hyponatraemia. Water intoxication can be reversed by stopping the drug, and witholding water.

In postprandial hypotension large meals should be avoided; instead small meals with low carbohydrate content should be eaten at frequent intervals. Drinking coffee after meals may help. Caffeine blocks vasodilatatory adenosine receptors. A dose of 250 mg (present in two cups of typical espresso) can be used. Tolerance may develop. The somatostatin analogue, octreotide (25 or 50 μg, ideally 30 minutes before food) prevents postprandial hypotension by inhibiting release of a variety of vasodilatatory gastrointestinal peptides. It also may reduce postural and exercise-induced hypotension. Side effects include abdominal colic and loose stools which respond to spasmolytics (Buscopan) and opiates (codeine phosphate and loperamide). Octreotide does not appear to enhance supine nocturnal hypertension.

Anaemia worsens symptoms of orthostatic hypotension and may occur in PAF and with renal impairment, in diabetes mellitus and in systemic amyloidosis. Erythropoietin (given subcutaneously) stimulates red cell production, raises red cell mass and haemoglobin levels. This reduces orthostatic hypotension and its symptoms in such situations.

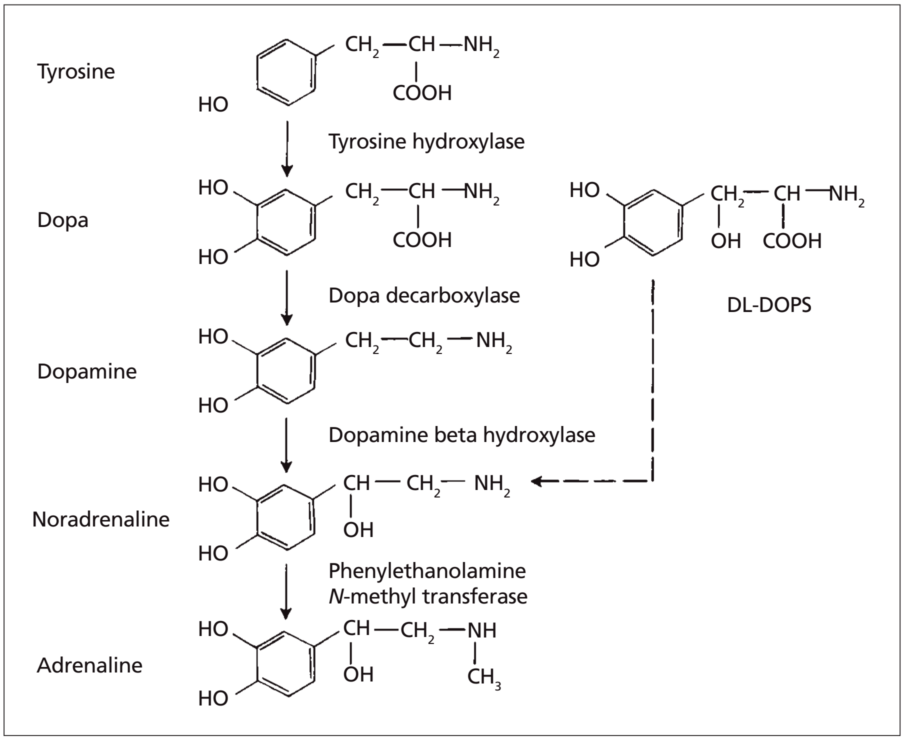

Tyrosine
Tyrosine hydroxylase
Dopa
Dopa decarboxylase
Dopamine
Dopamine beta hydroxylase
Noradrenaline
Phenylethanolamine N-methyl transferase
Adrenaline
DL-DOPS

Figure 23.22 Biosynthetic pathway in the formation of adrenaline and noradrenaline. The structure of DL-DOPS is indicated on the right. It is converted directly to noradrenaline by dopa decarboxylase, thus bypassing dopamine β-hydroxylase. (From Mathias *et al*. 1990, with permission.)

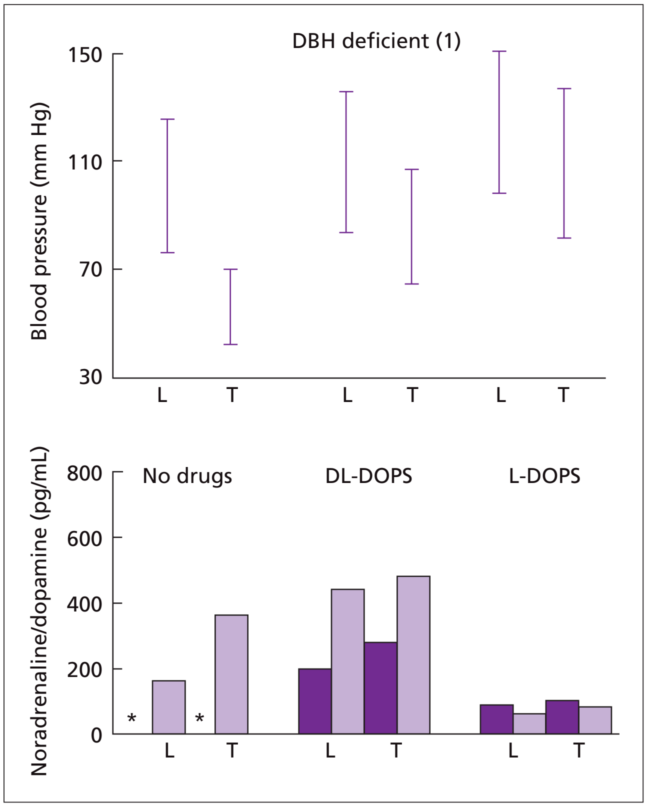


Figure 23.23 Blood pressure (systolic and diastolic) while lying (L) and during head-up tilt (T) in one of two siblings with dopamine beta hydroxylase (DβH) deficiency (1) before, during and after treatment with DL-DOPS (racemic mixture; DOPS, dihydroxyphenylserine) and L-DOPS (laevo form). The laevo form causes a greater rise in blood pressure and a greater reduction in postural hypotension than the racemic mixture. (From Mathias *et al*. 1990, with permission.)

Table 23.11 Drugs used for reducing hypertension in autonomic dysreflexia.

Afferent		Topical lidocaine
Spinal cord		Clonidine* Reserpine* Spinal anaesthetics
Efferent	Sympathetic ganglia	Hexamethonium
	Sympathetic nerve terminals	Guanethidine
	Alpha-adrenoceptors	Phenoxybenzamine
Target organs	Blood vessels	Glyceryl trinitrate Nifedipine

* Clonidine and reserpine have multiple effects, some of which are peripheral.

Table 23.12 Management strategy in autonomic failure.

Specific

For orthostatic hypotension, and bladder, bowel, sexual dysfunction: non-pharmacological and pharmacological therapy
For respiratory abnormalities: consider tracheotomy
For oropharyngeal dysphagia: consider PEG
For depression: drug treatment

General education

Of patients and partners, relatives, carers, medical practitioners, supportive therapists, to include physiotherapists, occupational therapists, speech therapists and dietitians

Patient support groups

To disseminate information and increase awareness:
Autonomic Disorders Association, Sarah Matheson Trust in UK
Shy–Drager Association in USA

Autonomic nurse specialist or autonomic liaison nurse

To link, coordinate and streamline specialist care with the patient, carers and community

PEG, percutaneous endoscopic gastrostomy.

Difficulties in the management of orthostatic hypotension have resulted in an array of drugs that have been reported to provide benefit in individual cases or in certain disorders (Tables 23.11 and 23.12). As with all drugs they should be used cautiously. Some have serious side effects such as cardiac failure with pindolol, and gastric ulceration and haemorrhage with indometacin. The use of a noradrenaline pump in extreme cases has been used with benefit.

Drugs should be used to reduce the side effects of therapy that is essential for associated disease. When levodopa is used to treat parkinsonism, higher doses of dopa-decarboxylase inhibitors should be used. The dopamine antagonists metoclopramide and domperidone also reduce the peripheral effects of dopamine.

Supine hypertension

Supine hypertension occurs frequently in PAF and may be worsened by drug treatment. It is unclear if certain drugs, such as higher doses of fludrocortisone are more likely to cause it. Supine hypertension may increase symptoms of cerebral ischaemia during postural change through an unfavourable resetting of cerebral autoregulatory mechanisms. Head-up tilt especially at night is probably the most practical method to prevent nocturnal supine hypertension. Omission of the evening dose of vasopressor agents, a pre-bedtime snack or alcohol to induce postprandial hypotension, and sometimes even use of short-acting antihypertensive drugs should be considered.

The long-term possible effects of supine hypertension include cardiac hypertrophy and damage to subcortical cerebral vessels. This may occur in PAF; these patients have a good prognosis and drugs may be used over many years. The benefits of treating orthostatic hypotension effectively, thus reducing the likelihood of trauma and improving their quality of life, should be weighed against the long-term risks.

Neurally mediated syncope

Management is dependent on the cause, provoking factors, disability caused and whether the episodes are of the cardio-inhibitory, vasodepressor or mixed type. Vasovagal syncope usually carries an excellent prognosis. Once the diagnosis is confirmed, an important component is positive reassurance. Advice on non-pharmacological measures includes ensuring salt repletion, an adequate fluid intake and techniques to enhance sympathetic activity and prevent pooling. The former include the use of isometric hand exercise and the latter activation of the calf muscle pump. If necessary subjects should lie flat with the legs upright or with the head between the knees. Each subject should decide on which methods to use effectively in different situations. This is of particular value when there is a window of warning before the loss of consciousness. In vasodepressor syncope low-dose fludrocortisone and sympathomimetics can be used if needed. Ephedrine is contraindicated if tachycardia is a problem; midodrine is the alternative. In those with a predominant cardio-inhibitory component, a demand pacemaker needs consideration especially when there is minimal warning before fainting. Cognitive behavioural psychotherapy is helpful if there is coexisting phobia, panic attack or anxiety disorder. 5-HT and noradrenaline uptake inhibitors such as fluoxetine, sertraline and venlafaxine have also been used.

In carotid sinus hypersensitivity, a cardiac demand pacemaker often is needed in the cardio-inhibitory and mixed forms. When the vasodepressor component is present and persists following pacemaker insertion, vasopressor agents including midodrine should be considered. Caution should be exercised as these patients often are elderly and may have vascular disease and prostatic hypertrophy that may increase the tendency to side-effects. In unilateral hypersensitivity, carotid sinus denervation is sometimes carried out.

In situational syncope, management should be directed towards the underlying cause and pathophysiological basis. In micturition syncope, occuring mainly in males, advice is needed to avoid contributing factors (e.g. alcohol). The bladder should be emptied while sitting rather than standing, especially if the patient has to pass urine during the night.

Postural tachycardia syndrome

These patients often need a combination of measures. Tachycardia often is associated with a low supine level of blood pressure, and a substantial number also have vasovagal syncope. Treatment is similar to the vasodepressor form of vasovagal syncope, with non-pharmacological measures and if needed drugs such as fludrocortisone and sympathomimetics. Ephedrine is contraindicated. Midodrine does not cause tachycardia and is the sympathomimetic of choice. Beta-adrenoceptor blockers, especially cardioselective ones such as bisoprolol, have a role. A selective sinus node blocker, ivabradine, has also been used to reduce tachycardia.

Hypertension

Hypertension resulting from increased sympathetic nervous activity in the Guillain–Barré syndrome and following subarachnoid haemorrhage may respond to propranolol and sympatholytic agents. In high spinal cord injuries, determining and rectifying the provoking cause of autonomic dysreflexia is crucial, as the key is prevention. A range of drugs, based on knowledge of the pathophysiological mechanisms, can be used to prevent or reduce hypertension in such patients (Table 23.11).

Sudomotor disorders

Anhidrosis

The ensuing problems include dry skin, hyperthermia and vasomotor collapse in hot weather. Dry skin is helped by suitable emollients. Prevention of hyperthermia is important by avoiding exposure to heat and ensuring a suitable micro-environment, ideally by air conditioning. Mechanisms to aid heat loss include tepid sponging to aid evaporation, fans to enhance convection loss and the ingestion of cool drinks. In severe hyperpyrexia, immersion in a cold bath may be needed.

Hyperhidrosis

Management depends upon the underlying cause, the sites involved and the functional and emotional disability. In hyperhidrosis over the palms and soles, local application of astringents containing glutaraldehyde and antiperspirants containing aluminium salts may reduce sweating as does iontophoresis. Low-dose oral pharmacotherapy includes anticholinergics (probantheline bromide 15 mg t.d.s) and centrally acting sympatholytics (clonidine 25–50 μg t.d.s). Side effects include a dry mouth. Glaucoma should be excluded prior to use of anticholinergics. Clonidine may reduce facial flushing. Topical anticholinergic cream (hyoscine hydrobromide or glycopyrrolate) may be helpful over small areas. Botulinum toxin is successful in hyperhidrosis affecting the axillae, palms and face. Injections may need to be repeated.

When these measures fail, surgical intervention using percutaneous endoscopic transthoracic sympathectomy, with ablation of prevertebral sympathetic ganglia from T2 to T4 should be considered. Ablation of T1/T2 also is used in facial flushing. In some, compensatory hyperhidrosis below the anhidrotic region can be extremely troublesome.

Alimentary system

Xerostomia is helped by artificial saliva. Excessive salivation responds to botulinum injection. Achalasia of the oesophagus may require dilatation, botulinum injection or surgery. In MSA with oropharyngeal dysphagia, advice should be provided on the type and consistency of food; severe dysfunction increases the risk of tracheal aspiration and a feeding percutaneous gastrostomy may be needed.

The dopamine antagonists metoclopramide and domperidone increase gastric emptying in gastroparesis, as does the macrolide erythromycin which stimulates motilin receptors. Peptic ulceration occurs in the early stages after high spinal cord injury and prophylaxis includes H_2 antagonists (cimetidine and ranitidine) and proton-pump inhibitors (omeprazole).

In diarrhoea caused by bacterial overgrowth, as in the blind loop syndrome, broad-spectrum antibiotics (neomycin or tetracycline) may be the initial step before using codeine phosphate or other opiate-based antidiarrhoeal agents. Octreotide, the somatostatin analogue, can reduce diarrhoea in amyloidosis and diabetic autonomic neuropathy. Aperients and laxatives, together with a high-fibre diet, are needed in constipation.

Urinary tract

In outflow tract obstruction, procedures which include prostatectomy, transurethral resection or sphincterotomy may be needed. Surgical procedures often induce or worsen incontinence in MSA. Bladder dysfunction may be helped by drugs that influence detrusor muscle activity (anticholinergics) or sphincter malfunction (alpha-adrenergic blockers). Intermittent or in-dwelling catheterization may be necessary. Nocturia in PAF is often helped by intranasal or oral desmopressin given in the evening.

Sexual function and the reproductive system

Erectile failure in men can be treated by suction devices, an implanted prosthesis or drugs. The latter can be given locally (intracavernosal or urethral) or orally (sildenafil). Sildenafil and allied drugs have the potential through vasodilatation to lower blood pressure substantially, especially in patients with orthostatic hypotension. In DβH deficiency, difficulty in ejaculation is improved by treatment with DOPS. Pregnant women with high spinal injuries may develop severe hypertension with cardiac dysrhythmias and eclampsia during uterine contractions and delivery. Spinal anaesthesia, which reduces spinal sympathetic discharge, often permits a normal delivery.

Respiratory system

A tracheostomy may be necessary in severe inspiratory stridor resulting from laryngeal abductor paresis, especially when oxygen desaturation occurs at night. With periodic apnoea, timed or triggered bilevel positive airway pressure ventilation may be useful. In high spinal cord lesions on artificial ventilation particular care should be taken during tracheal suction and toilet to avoid bradycardia and even cardiac arrest. In ventilated tetanus patients, the reverse – tachycardia and hypertension – may occur.

Eye and lacrimal glands

In alacrima, tear substitutes such as hypromellose eye drops are needed. Cycloplegia can be reduced by local cholinomimetics. Patients should be made aware of night blindness in sympathetic denervation and about a low threshold to sunlight in parasympathetic denervation.

Treatment in MSA and Parkinson's disease

In the parkinsonian forms of MSA, levodopa is sometimes of benefit in the early stages. However, it may cause or enhance orthostatic hypotension and should be used with higher doses of dopa decarboxylase inhibitors. The monoamine oxidase-B inhibitor, selegiline, has been used in combination with levodopa and also may worsen orthostatic hypotension. It may cause hypotension also in Parkinson's disease by mechanisms that include the central effects of its metabolites, methyl-amphetamine. Amantidine may provide motor benefit without lowering blood pressure. Dopaminergic agonists may be effective but it is unclear if they worsen orthostatic hypotension. With time there often is refractoriness to anti-parkinsonian drugs in MSA. There is no effective pharmacotherapy for cerebellar deficits in MSA. Supportive therapy using disability aids should be provided.

The management of autonomic dysfunction needs to consider local organ dysfunction, the underlying or associated disease and integrative components often needing specialist care (Table 23.12).

Of particular importance, especially in the generalized disorders, is the need for a holistic approach which includes the management of the autonomic deficits and the underlying disorder. Management should involve not only the patient, but the family, carers and community.

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24 Uro-Neurology

Clare Fowler, Sohier Elneil

Neural control of the uro-genital system

Because voluntary control over the uro-genital system is critical to our social existence and its peripheral innervation derives from the most distal segments of the spinal cord, the importance of the integrity of long tracts of the central nervous system for physiological function is immediately apparent (Figure 24.1). In clinical practice, as shown in a survey of the site of the underlying neurological disease affecting a sample of patients referred to the department, spinal cord involvement of various pathologies is the most common cause of bladder symptoms (Figure 24.2).

It might be supposed that because of the commonality of innervation shared by the bladder and genital organs, that abnormalities of these two systems inevitably occur together. However, this is not the case, because although the organs share the same root innervation and have common peripheral nerves within the pelvis, each is controlled by its own unique set of central nervous system reflexes.

In this chapter a brief account of the neurophysiological control of the bladder is given, followed by a description of the effect that neurological disease at different levels of the nervous system may have and the management of those conditions. Sexual function and neurogenic sexual dysfunction are covered in the same way.

Bladder function and its neurological control

Physiology

The bladder performs only two functions, storage and emptying, with control of these two mutually exclusive activities at two different anatomical locations. Storage is organized within the spinal cord and micturition results from activation by suprapontine influences of a centre in the dorsal tegmentum of the pons, the pontine micturition centre (PMC) (Figure 24.1). Some of the proposed anatomical pathways are outlined in Chapter 2.

In recent years functional brain imaging has contributed greatly to our understanding of the cortical input into bladder control. During the storage phase, raised pressure within the bladder outlet is maintained by sympathetic influences on the smooth muscle of the detrusor in the bladder neck region and by pudendal nerve activation of the striated muscle of the urethral sphincter and the pelvic floor. Inhibition of the parasympathetic outflow prevents detrusor contraction. Behaviourally, throughout the storage phase, our perception of bladder fullness enables us to make the necessary planned strategies to achieve the next appropriately located void before reaching an uncomfortable degree of bladder distension or the sensation of 'severe urge to void'.

Several functional brain imaging experiments have examined cortical activity during continent storage and a consistent finding of all these studies is that there is an activation of the periaqueductal gray (PAG) during bladder filling (for review see Kavia *et al.* 2005; Figure 24.3). This is in keeping with experimental studies in the cat, and it is thought that the PAG serves as a central relay centre for afferent activity from the pelvic organs and is an interface between the afferent and efferent limbs of bladder control circuits, 'informing' the PMC about the degree of bladder fullness. The PAG has multiple connections with higher centres such as the thalamus, insula, cingulate and prefrontal cortices. Activation of the insula is consistent with what is known about regions of activation involved in interoceptive awareness of visceral sensations.

The prefrontal cortex, the seat of planning complex cognitive behaviours and of appropriate social behaviours, is activated on bladder filling and it seems likely that this region of the brain is involved in the conscious and social control of the bladder function. It has been proposed that the task of the prefrontal cortex is to make a decision as to whether or not micturition should take place at a particular place or time.

With the decision to void, activation is seen in the prefrontal, insula, hypothalamus and PAG and the PMC. Activation of the

Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

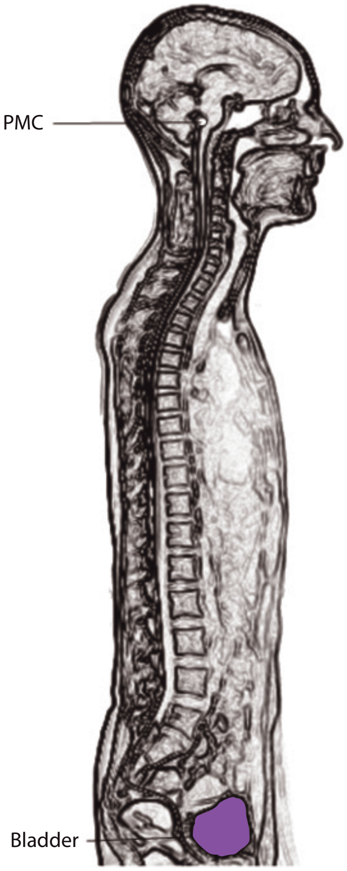
PMC
Bladder

Figure 24.1 Saggital MRI of man showing innervation of genito-urinary system–pontine micturition centre (PMC) to bladder.

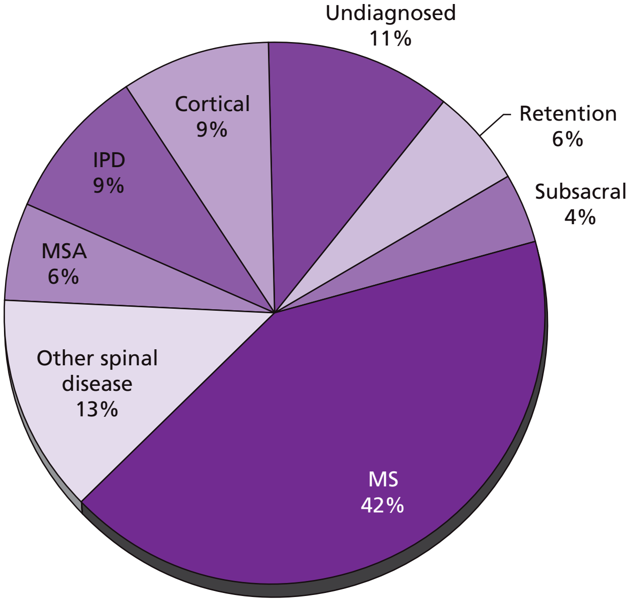

Figure 24.2 Neurological causes of bladder disorders in a small sample of patients presenting to the uro-neurology department. IPD, idiopathic Parkinson's disease; MSA, multiple system atrophy; MS, multiple sclerosis.

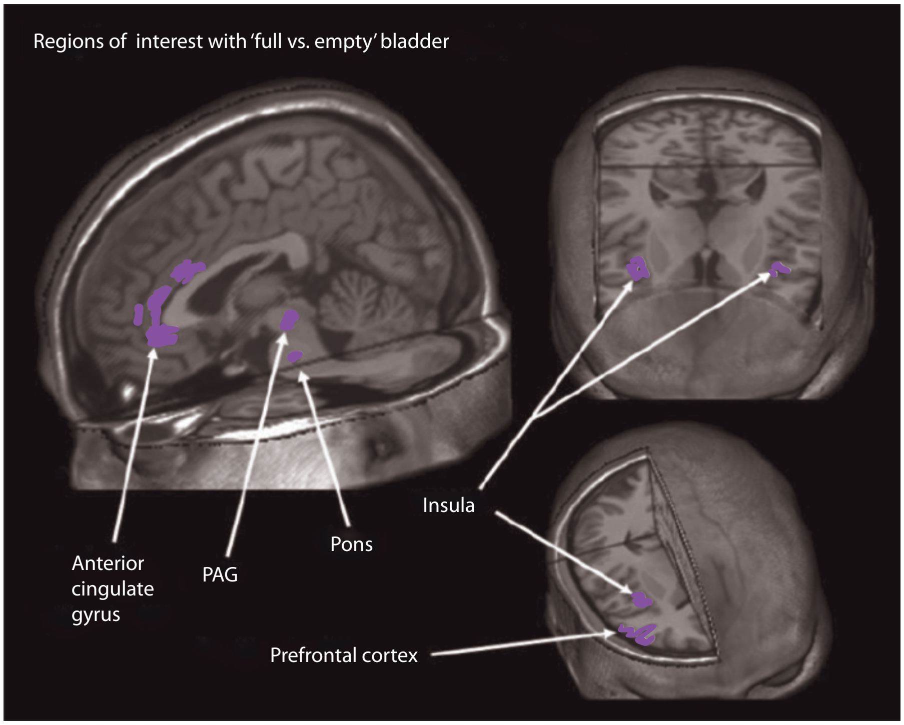
Regions of interest with 'full vs. empty' bladder
Insula
Pons
Anterior cingulate gyrus
PAG
Prefrontal cortex

Figure 24.3 Summary of regions of interest comparing 'full vs. empty' bladder conditions based on the coordinates published in five positron emission tomography (PET) studies (Athwal *et al*. 2001; Blok *et al*. 1997, 1998; Matsuura *et al*. 2002; Nour *et al*. 2000). The figure from Kavia *et al*. (2005) was prepared using MRIcro (Rorden & Brett 2000) with permission from *Journal of Comparative Neurology*.

PMC is the final brain efferent nucleus and in health results in spinal transmission of activity to sacral segments of the spinal cord. Voiding is achieved by relaxation of the urethral sphincter followed some seconds later by a contraction of the bladder, resulting in an increase in bladder pressure and the flow of urine. Relaxation of the urethral smooth muscle is mediated by activation of the parasympathetic pathway to the urethra which triggers the release of nitric oxide and by the removal of adrenergic and somatic cholinergic excitatory inputs. Secondary reflexes elicited by flow of urine through the urethra facilitate bladder emptying.

Neurological causes of bladder dysfunction

Cortical disease

The importance of the anterior regions of the frontal lobes in bladder control was established by Dr Peter Nathan, the first uro-neurologist at Queen Square, and Mr John Andrew, a neurosurgeon at the Middlesex Hospital, in a paper published in *Brain* in 1964. A series of patients was reported with disturbed bladder control from various frontal lobe pathologies including tumours, damage following rupture of an intracranial aneurysm, penetrating brain wounds or the iatrogenic damage of leucotomy. The typical clinical picture was of a patient with severe urgency and frequency of micturition and urge incontinence, who is both socially aware and embarrassed by their incontinence. Only if frontal lobe pathology is more extensive, causing loss of social inhibition, do patients become unconcerned about their loss of bladder control.

Subsequent authors reported the occurrence of urinary incontinence in patients with frontal lobe lesions from a number of different pathologies. Recently, there has been a detailed analysis of the bladder symptoms of two patients with resected gliomas involving the posterior part of the right cingulate gyrus and the right inferior frontal cortex and insula, respectively, with an interesting discussion as to what insight these cases give about the cortical control of continence.

Urinary retention has occasionally been described in patients with brain lesions. In the series by Andrew and Nathan two of their patients were in urinary retention at some stage and there have been a small number of case histories of patients with right frontal lobe pathology with urinary retention.

Cerebrovascular disease

Incontinence following stroke is not a straightforward problem. Cystometric studies in series of patients following stroke generally conclude that detrusor over-activity (DO) is the most common urodynamic abnormality, although acute urinary retention may occur at the onset. There does not appear to be any definite lateralization of lesions causing DO, although possibly the pathology is more often right-sided, nor are there any specific locations; however, anteriorly situated damage is more likely to result in incontinence (Figure 24.4). At admission, approximately 50% of

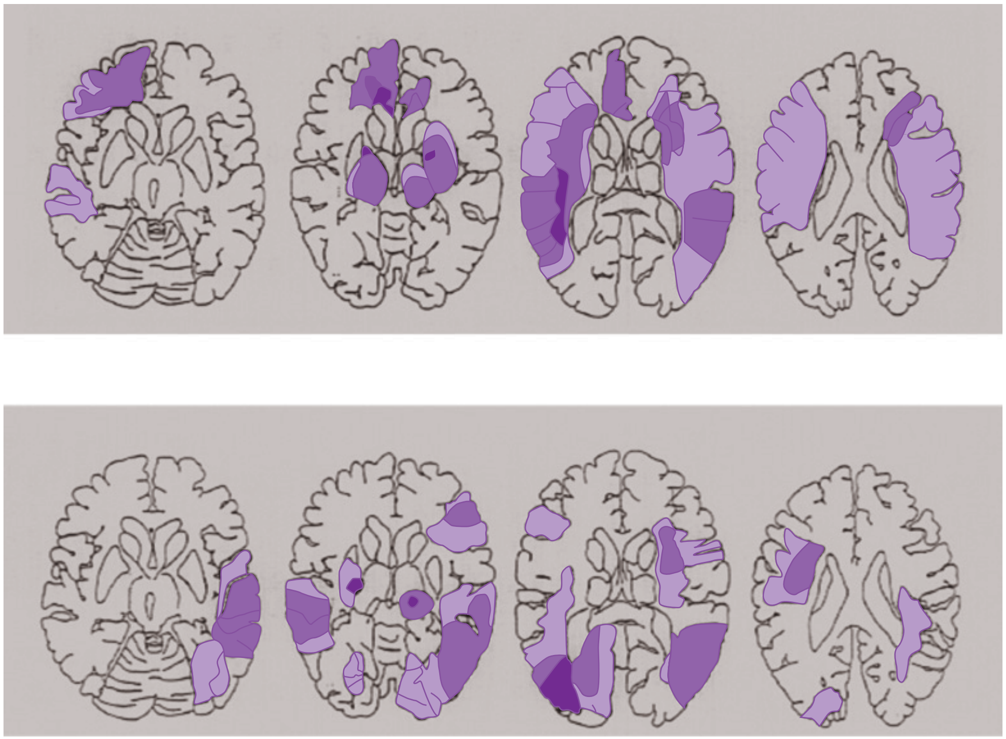

Figure 24.4 Lesions on brain CT or MRI with micturitional disturbance (upper panel) and without (lower panel) (Sakakibara *et al.* 1996).

stroke patients will have incontinence, but the incidence declines over the following 6 months to approximately 5%. Long-term incontinence is commonly caused by DO and is seen in patients with severe neurological deficits (aphasia and dysphagia, particularly) and a high level of persistent disability.

The other approach to looking at stroke and urinary incontinence has been epidemiological. Following a stroke the presence of urinary incontinence within 7 days appears to be the most powerful prognostic indicator for poor survival and eventual functional dependence, more so than a depressed level of consciousness in this period. The explanation for this is not known but it has been suggested that either incontinence is the result of a severe general rather than specific loss of function, or that those who remain incontinent are less motivated, both to recover continence and more general function.

Dementia

Urinary incontinence in dementia is acknowledged to be a major socio-economic problem of ever-increasing proportions. In fact it is a complex problem. Incontinence in the frail elderly is common and has many potential causes. In a large group of elderly patients who were institutionalized because of their general frailty, the same variety of underlying pathophysiologies was found in those with mental impairment as those without. Although DO was the most common cause of incontinence in all cases, in 40% there were other causes and in nearly one-third incontinence was related to disorders of the urethral outlet, i.e. potentially surgically correctable conditions.

There is also convincing evidence of a specific disorder of the detrusor muscle characterized by ultra-structural changes that has an increasing incidence in the elderly. This is thought to result in DO and incomplete emptying, the so-called 'detrusor hyperactivity with impaired contractile function' (DHIC). It seems highly likely that with loss of general 'coping abilities' because of mental impairment this becomes a prominent cause of incontinence.

The role of cortical brain disease is unclear. Frontal lobe pathology would be expected to cause DO and there is some evidence that this is a contributing factor. One of the differences between symptoms in those with and those without dementia is that urgency preceding episodes of incontinence is more frequently reported by those without.

In a study of patients with cognitive decline, incontinence was associated with severe mental failure in pure Alzheimer's disease but preceded cognitive impairment in diffuse Lewy body disease. A much less common cause of dementia, low-pressure hydrocephalus, has incontinence as a cardinal feature; improvement in cystometric function has been demonstrated within hours of lumbar puncture in patients with this disorder.

Since the advent of cholinesterase inhibitors to treat symptoms in mild to moderate dementia, it is not uncommon to find a patient on such a treatment who has also been prescribed an antimuscarinic to treat their urinary urgency. No systematic study has yet been published that looks at interactions of these medications, but on theoretical grounds it would seem sensible to use an antimuscarinic to treat the bladder that does not cross the blood–brain barrier, such as tolterodine or trospium chloride or possibly the M3 specific antimuscarinic, darifenacin (Table 24.1). There are as yet no published data showing that the cholinesterase inhibitors cause or exacerbate bladder dysfunction.

Bladder dysfunction in Parkinson's disease

Bladder symptoms are being recognized amongst the non-motor aspects of Parkinson's disease (PD) which are thought to be the consequence of the widespread dopaminergic and non-dopaminergic neurodegeneration that occurs in the condition. The resulting 'vegetative symptoms' have a very negative impact on the patient and their carer as the condition advances.

Table 24.1 Anticholinergic agents used to treat symptoms of detrusor over-activity.

Generic name	UK trade name	Dose (mg)	Frequency	Receptor subtype selectivity	Elimination half-life of parent drug (hour)
Propantheline bromide	Pro-Banthine®	15	t.d.s.	Non-selective	<2
Tolterodine tartrate	Detrusitol®	2	b.d.	Non-selective	2.4
Tolterodine tartrate	Detrusitol® XL	4	o.d.	Non-selective	8.4
Trospium chloride	Regurin®	20	b.d.	Non-selective	20
Oxybutynin hydrochloride	Ditropan®	2.5–5	b.d. to q.d.s.	Non-selective	2.3
Oxybutynin hydrochloride XL	Lyrinel® XL	5–30	o.d.	Non-selective	13.2
Propiverine hydrochloride	Detrunorm®	15	o.d. to q.d.s.	Non-selective	4.1
Darifenacin	Emselex®	7.5–15	o.d.	Selective muscarinic M3 receptor antagonist	3.1
Solifenacin succinate	Vesicare®	5–10	o.d.	Selective muscarinic M2 and M3 receptor antagonist	40–68

b.d., twice daily; o.d., once daily; q.d.s., four times daily; t.d.s., three times daily.

How common are bladder symptoms in patients with clearly defined idiopathic PD is uncertain. It has been claimed that the prevalence is 38–71% but some of those early studies of prevalence were based on patients presenting in urology clinics, in elderly patient populations or were published before the diagnosis of multiple system atrophy (MSA) was recognized as often as it is today. In the most recent study of patients with PD diagnosed according to modern criteria, and using validated questionnaires, the prevalence of urinary symptoms was found to be 27–39%, considerably higher than in healthy controls. A clear correlation with the neurological disability and stage of disease has been demonstrated suggesting a relationship between dopaminergic degeneration and symptoms of urinary dysfunction.

Typically, PD patients with bladder dysfunction present with advanced neurological disease and describe how the bladder symptoms came on many years after treatment for PD started. Cystometric testing commonly shows a reduced capacity and DO, usually with complete emptying although sometimes an apparently obstructed voiding picture may be seen. It was suggested that there may be an impaired relaxation or 'bradykinesia' of the urethral sphincter which could be reduced by subcutaneous apomorphine. The most common complaint is of nocturia and urinary urgency, and then urgency incontinence may occur if poor mobility compounds the bladder disorder. A particular difficulty arises because symptoms of outflow obstruction may also occur in males with PD, making the distinction between neurogenic and bladder outflow obstruction resulting from benign prostatic enlargement difficult. The reputation for a poor outcome following prostatic surgery in men with PD is probably because of the inclusion of some patients with MSA in studies of 'Parkinson's disease and the bladder'. If there is convincing evidence of prostatic occlusion and obstructed voiding on cystometry, a prostatectomy should be considered, bearing in mind that some men with PD certainly do benefit from transurethral resection of the prostate (TURP).

The commonly accepted hypothesis to explain bladder symptoms in PD is that degeneration of dopaminergic neurones leads to loss of the substantia nigra tonically D1 mediated inhibition of the PMC. Detrusor over-activity (DO) has been demonstrated in experimentally induced parkinsonism in marmosets, and selective dopamine D1 receptor agonists alleviated the abnormality. In rats experiments have shown that dopaminergic neurones originating in the ventral tegmental area (VTA) control the micturition reflex biphasically, with a facilitatory effect from low-dose stimulation of dopamine D2 receptors, while high-dose stimulation of the dopamine D1 receptors has an inhibitory effect on micturition. Patients with PD and bladder symptoms have less uptake of a radionuclide tracer of dopamine transport in the striatum than patients with PD but without bladder dysfunction, indicating a correlation between urinary dysfunction and degeneration of the nigrostriatal dopaminergic cells. Furthermore, recent studies have shown that the presence of bladder symptoms is related to the decrease in the total number of dopaminergic neurones in the striatum and that relative degeneration of the caudate correlates with severity of symptoms.

The effect of anti-parkinsonian medication on bladder function is complex and studies that have looked at the effect of levodopa or apomorphine on bladder behaviour have produced conflicting results. In one small study, DO was reduced after administration of apomorphine and, to a lesser extent, levodopa, but in another study with patients of more advanced disease showing 'on–off' phenomena, DO lessened with levodopa in some patients and worsened in others. The most recent study suggests that in advanced PD, levodopa exacerbates DO in the filling phase, but also improves bladder emptying through increased detrusor contractility, so that the post-micturition residual volumes diminish. The effects of medication on bladder control may be complex and it has been suggested that the effect of dopamine occurs through cortical mechanisms, as part of the improvement in ability to separate and integrate sensory input.

Multiple system atrophy

MSA seems to selectively involve neural components specifically involved in the innervation of the uro-genital tract; bladder control may therefore be affected early in the course of the disease, usually occurring before symptoms and signs of postural hypotension. Corticotrophin-releasing factor staining cells in the pontine region have been shown to undergo selective atrophy and it has been postulated that these cells are in the region of the pontine micturition centre (PMC). Axons of the intermediolateral cell column conveying autonomic innervation to the sacral segments are known to atrophy, as do the anterior horn cells in Onuf's nucleus which innervate the sphincters. SPECT studies have shown reduced cerebellar vermis activation during urinary storage and micturition in MSA.

The functional effects of these deficits include DO, incomplete emptying, an open bladder neck in men and sphincter weakness, all compounding to produce early and severe incontinence. Incomplete emptying to a significant degree commonly occurs (unlike the situation in PD), although the symptoms are predominantly those of incontinence. Very occasionally, a complete failure to void, i.e. retention, can be a presenting clinical feature in both men and women. Bladder dysfunction may change during the progression of MSA, with a progressive reduction in the degree of DO and increasingly high post-micturition residual volume. This is a situation that is highly amenable to treatment and many patients with MSA can regain bladder control for several years before their general neurological disability becomes overwhelming.

The role of sphincter EMG in recognizing the re-innervation, secondary to the loss of anterior horn cells in Onuf's nucleus in MSA, has been contentious. One of the authors (C.F.) has been a proponent of the value of the investigation if found to be highly abnormal in a patient with early parkinsonism or in patients with a cerebellar syndrome of late onset, a view shared by some others. In a retrospective post-mortem study, although a very high proportion of patients who were subsequently shown to have died of

MSA had had an abnormal sphincter electromyogram (EMG) – often quite early in the course of their disease – sufficient EMG data were lacking on patients who had alternative diagnoses, including PD, for the specificity of the test to be calculated. Other groups have shown sphincter EMG abnormalities in patients with long-standing PD while others purport to find no difference between patients with MSA and PD. The test is clearly method-sensitive and centres that carry out individual motor unit analysis by manual methods seem to find it more valuable than those that use an automated analysis technique.

Bladder symptoms in other parkinsonian syndromes are less prominent and although they may occur as part of the patient's general disability are rarely so severe or occur at a stage of the disease when a neurological diagnosis is not clearly evident.

Brainstem lesions

The location of the micturition centre in the pons means that occasionally pathology affecting the dorsal tegmentum may result in disturbances of micturition, most commonly difficulties voiding. Voiding difficulty is a rare but recognized symptom of a posterior fossa tumour in children and has been reported in series of patients with brainstem pathologies including strokes. An analysis of urinary symptoms of 39 patients who had brainstem strokes showed that lesions that resulted in disturbance of micturition were usually dorsally situated. There have also been a number of sporadic case reports describing urinary retention resulting from brainstem lesions. The proximity in the dorsal pons of the medial longitudinal fasciculus to the pontine micturition centre means that an internuclear opthalmoplegia is highly likely in patients with pontine pathology causing a voiding disorder.

Spinal cord disease and multiple sclerosis

Spinal cord pathology is the most common cause of neurogenic bladder dysfunction (Figure 24.2). The possible pathophysiological consequences of spinal lesions on bladder function are several and are summarized in Table 24.2.

Following disconnection of the sacral cord from brainstem centres new spinal segmental reflexes emerge which drive detrusor contraction and cause the abnormality of DO, which underlies the symptoms of urgency, frequency and urge incontinence. Immediately following spinal cord transection and during the phase of spinal shock the bladder is acontractile but, gradually over the course of some weeks, reflex detrusor contractions develop in response to low volumes of filling. The neurophysiology of this recovery has been studied in the cat and it has been proposed that following spinal injury, formerly quiescent C fibres emerge as the major afferents of the aberrant reflex. It is assumed that the same pathophysiology occurs in humans and the response to intravesical capsaicin (a C fibre neurotoxin) of patients with multiple sclerosis (MS) supports this view. The same spinal lesion that causes the emergence of this reflex often causes upper motor neurone symptoms and signs in the lower limbs, and urge incontinence is particularly likely to affect patients with spastic paraparesis and DO. This is the basis of a valuable clinical point: when considering whether or not a patient has a neurogenic bladder resulting from spinal cord involvement – an absence of neurological signs in the legs makes such a diagnosis unlikely.

Spinal pathways that connect the PMC to the sacral cord and affect the reciprocal activity of the detrusor and sphincter are crucial for the coordinated activity of bladder storage and voiding. Following disconnection from the pons, the synergistic activity between sphincter and the detrusor is lost; the result is that the sphincter tends to contract when the detrusor is contracting, a condition known as 'detrusor–sphincter dyssynergia'. This, together with poor neural drive on the detrusor muscle during attempts to void, means that there is likely to be incomplete bladder emptying which may in turn exacerbate the symptoms caused by DO. Although the neurological process of voiding may have been as equally severely disrupted by spinal cord disease as the process of storage, the symptoms of difficulty emptying are relatively minor compared to those of urge incontinence. Often it is only on direct questioning that a patient will admit to difficulty initiating micturition or an interrupted stream, or possibly a sensation of incomplete emptying.

Spinal cord injury

Following spinal cord injury (SCI), DO, loss of compliance (the expansile property of the bladder) and detrusor–sphincter

Table 24.2 The possible pathophysiological consequences of spinal lesions on bladder function.

	Dysfunction	Symptoms
Detrusor overactivity	Detrusor muscle develops involuntary contractions at low filling volumes	Urgency Frequency Urge incontinence
Detrusor–sphincter dyssynergia	Contraction of the sphincter as the detrusor contracts	Interrupted stream Incomplete bladder emptying
Upper motor neurone lesion of sphincter and pelvic floor	Loss of central connections	Difficulty with voluntary initiation Inability to suppress urge and so urge incontinence

dyssynergia (DSD) can be of such severity as to cause ureteric reflux, hydronephrosis and eventual upper renal tract damage. Before the introduction of modern treatments, renal failure was a common cause of death following SCI. The bladder problems of those with SCI must therefore be managed in such a way as to lessen the possibility of upper tract disease as well as provide the patient with adequate bladder control for a fully rehabilitated life. These patients need to remain under the care of an urologist who can arrange regular upper tract monitoring scans if necessary and it may be better for the patients, who are often young and have no progressive disease, to undergo definitive surgery on their lower urinary tract with a view to protecting the upper tracts and restoring continence. It was in patients with complete spinal cord transection that the 'Brindley stimulator', which applied electrical stimulation directly to each of the sacral roots, S2, 3 or 4 was implanted, with considerable clinical improvement but at the cost of section of the dorsal roots.

Multiple sclerosis

The pathophysiological consequences of MS affecting the spinal cord are similar to those of SCI, but the medical context of increasing disability is such that the patient's management must be quite different. In patients with MS there is a strong association between bladder symptoms and the presence of clinical spinal cord involvement including paraparesis, i.e. any upper motor neurone signs in the lower limbs. Furthermore, bladder symptoms become increasingly resistant to treatment as lower limb mobility deteriorates.

The most common urinary symptom is urgency and all series of urodynamic studies of patients with MS have shown that this is caused by underlying DO. However, patients may also volunteer or admit on direct questioning to difficulty with voiding such as hesitancy of micturition and an interrupted urinary stream. Evidence of incomplete emptying is commonly based on the patient's observation that having passed urine once, they are able to do so again within 5–10 minutes, rather than a reported sensation of continued fullness.

Unlike the bladder dysfunction that follows SCI, MS and other progressive neurological diseases very rarely cause upper renal tract involvement. This is even the case when long-standing MS has resulted in severe disability and spasticity. The reason for this is not known, but it means that in such diseases the emphasis of management needs to be on symptomatic relief.

Bladder dysfunction in other (non-traumatic) spinal cord diseases

A consistent feature of transverse myelitis is that although there may be an excellent clinical recovery from a tetraplegia of such severity that at its nadir artificial ventilation was necessary, bladder dysfunction is often the major residual neurological sequel. The explanation for this is not known but it may relate to the emergence of spinal segmental reflexes during the period of 'spinal shock' which then persist as a dominant functional mechanism. This observation must inevitably cause a certain degree of pessimism about the prospect of restoration of bladder function if 'spinal repair' becomes a reality.

DO occurs as an early feature and may even be a presenting symptom in patients with tropical spastic paraparesis caused by infection by human T-lymphotropic virus Type 1 (HTLV1) virus seen in Europe in patients of Caribbean origin.

Once a common cause of bladder dysfunction, neurosyphilis is now rarely seen but tabes dorsalis was classically said to result in an areflexic hyposensitive bladder because of involvement of the dorsal columns and roots, although a variety of abnormal urodynamic findings have been described.

Arteriovenous (AV) malformations of the spinal cord may be difficult to recognize clinically but commonly cause bladder disturbance as a prominent early feature. Although the majority of AV malformations occur in the thoraco-lumbar region, alterations to cord blood flow and subsequent conus ischaemia mean that the patient may present with what appears to be a conus or cauda equina lesion. Symptoms of voiding difficulty are common at an early stage and then urinary retention.

A mixture of upper and lower motor neurone signs in the legs together with urinary symptoms is characteristic of spinal dysrraphism and a tethered cord. Typically, asymmetric wasting of the calves and intrinsic muscles of the feet occurs, but the prominent bladder symptoms and possibly extensor plantar responses suggest a diagnosis of a conus lesion rather than peripheral neuropathy or previous poliomyelitis. Although the majority of cases present in childhood, it is a condition that should be considered even in adults with the appropriate clinical features. Urodynamic studies show a mixed picture of DO and incomplete bladder emptying, and although an improvement in bladder function following a de-tethering procedure has been claimed, the operation is usually carried out to treat pain or prevent progression of neurological deficit.

Conus or cauda equina lesions

Damage to the cauda equina and S2–4 roots leaves the detrusor 'decentralized' but not 'denervated' because the post-ganglionic parasympathetic innervation is unaffected. This may explain why the bladder dysfunction following a cauda equina lesion is unpredictable and even DO has been described. Loss of voluntary control is usually a symptom and there may also be pronounced defects of anal sphincter control with incontinent of flatus or liquid motions in addition to an inability to evacuate the bowel without digitation. Loss of control over bladder, bowel and loss of sexual function is particularly difficult for patients to bear psychologically when they are otherwise ambulant and mobile.

Although there are a number of series reporting the urodynamic changes that can occur following a cauda equina lesion, there has been no analysis of the effect a cauda equina lesion can have on the quality of life. However, the levels of compensation awarded in medico-legal cases reflect the fact that the loss of control of the pelvic organs resulting from a cauda equina injury is catastrophic.

Peripheral neuropathy

Diabetic neuropathy

Bladder involvement was once considered an uncommon complication of diabetes but the greater use of techniques for studying bladder function have shown that the condition is often asymptomatic and discovered incidentally. Bladder dysfunction in isolation does not occur and other symptoms and signs of generalized neuropathy must be present in affected patients. The onset of the disorder is insidious, with progressive loss of bladder sensation and impairment of bladder emptying over years, eventually culminating in chronic low-pressure urinary retention. It seems likely that there is involvement of both the vesical sensory afferent fibres causing reduced awareness of bladder filling and also of parasympathetic efferent fibres to the detrusor decreasing the ability of the bladder to contract.

Other neuropathies

About one-quarter of patients with Guillian–Barré syndrome have bladder symptoms. These usually occur in patients with more severe neuropathy and appear after limb weakness is established. Both detrusor areflexia and bladder over-activity have been described.

Recessively inherited Type II congenital sensory neuropathy (Chapter 9) and familial dysautonomias (Chapter 23) with involvement of small nerve fibres have bladder dysfunction amongst the disabilities.

Injury to pelvic nerves

The peripheral innervation of the pelvic organs can be damaged by extirpative pelvic surgery such as resection of rectal carcinoma, radical prostatectomy or radical hysterectomy. The dissection necessary in the surgery of rectal cancer is likely to damage the parasympathetic innervation to the bladder and genitalia as the pelvic nerves take a medio-lateral course through the pelvis either side of the rectum and the apex of the prostate. The nerves may either be removed together with the fascia that covers the lower rectum or may be damaged by a traction injury as the rectum is mobilized prior to excision.

Urinary incontinence following a radical prostatectomy or a radical hysterectomy that includes the upper part of the vagina, is probably also caused by damage to the parasympathetic innervation of the detrusor. In the case of a radical prostatectomy, there may be additional direct damage to the innervation of the striated urethral sphincter.

Myotonic dystrophy

Although myotonic EMG activity has not been found in the sphincter or pelvic floor of patients with myotonic dystrophy, bladder symptoms may be quite prominent and difficult to treat, presumably because of involvement of bladder smooth muscle. With advancing disease resulting from involvement of the internal anal sphincter, faecal incontinence may become a problem.

Management of incontinence

From the foregoing sections it will be evident that the most common bladder problem caused by neurological disease is a failure of storage and therefore incontinence. Because the bladder has such a limited repertoire of behaviour, incontinence can be the end product of several different pathophysiologies, but chief amongst these are either a failure of inhibition of the PMC because of a suprapontine cortical lesion, or the emergence of an abnormal segmental spinal reflex as a result of disconnection between the sacral cord and the pons because of spinal cord disease (Figure 24.1).

Although it is known that the pharmaceutical industry is researching a variety of agents that act at different sites of the ‘uroaxis’ to ameliorate DO, at the time of writing the major categories of drugs currently licensed are antimuscarinic agents. A serotonin/noradrenaline reuptake inhibitor, duloxetine, has been granted a provisional licence in Europe for the treatment of urinary stress incontinence but is still unlicensed. Detrusor injections of botulinum toxin A appear very promising to treat severe DO.

There is a hierarchy of treatment that may need to be employed as urinary incontinence worsens, e.g. with deteriorating spinal function in MS. The first line treatment uses antimuscarinics, if necessary then in combination with intermittent self-catheterization. If these measures are insufficient, detrusor injection of botulinum toxin would now be considered. These various treatments and interventions are described below.

Antimuscarinics (anticholinergics)

The premise for treatment of DO with an antimuscarinic agent was that this blocked the parasympathetic innervation effect on the M2/M3 receptors of the detrusor muscle. However, it is now being recognized that there may be a more complex mode of action active during the storage phase, and mediated through a muscarinic afferent mechanism, thus explaining the observed effects of increased bladder capacity and reduction of urinary urgency with treatment. There are now a number of such agents available (Table 24.1), and the long-acting extended-life (XL) formulations of these medications have the significant advantage of only needing to be taken once a day to provide 24-hour cover. Another potentially important difference between the various preparations is that the chemical structure of tolterodine and trospium renders them less lipophilic and therefore theoretically less likely to cross the blood–brain barrier and so result in fewer central adverse effects, although this has yet to be clearly demonstrated. Side effects of all these agents are common, a dry mouth in particular, and this reduces patient compliance. Other delivery systems have recently been developed in an attempt to reduce the side effects and these include intravesical instillation of anticholinergics such as oxybutynin and atropine. Dermal preparations of oxybutynin have also been shown to be better tolerated.

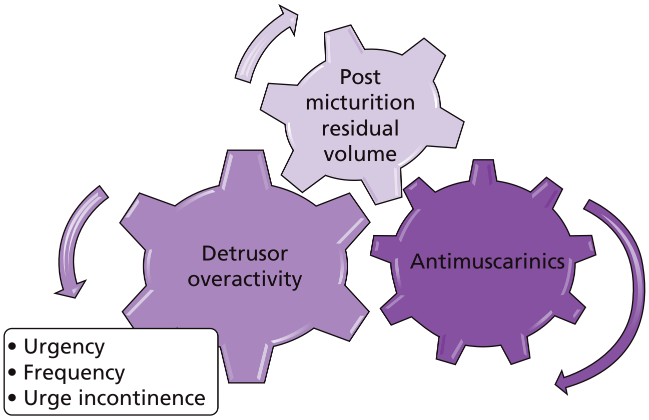

Figure 24.5 The importance of recognizing incomplete emptying is that any residual volume in the bladder can trigger volume-determined reflex detrusor contractions, exacerbating the clinical situation through worsening of the symptoms of frequency, urgency and urgency incontinence.

Management of incomplete bladder emptying

Prior to prescribing an antimuscarinic for patients complaining predominantly of symptoms of DO, it is important to measure their post-void residual (PVR) urine volume, particularly if the patient's symptoms suggest there is incomplete voiding. This can be performed with 'in–out' catheterization or alternatively using a small hand-held ultrasound device which many specialist nurse continence advisers now have access to. The importance of recognizing incomplete emptying is that any residual volume in the bladder can trigger volume-determined reflex detrusor contractions, exacerbating the clinical situation through worsening of the symptoms of frequency, urgency and urgency incontinence (Figure 24.5). If a symptomatic patient has a PVR volume of over 100 mL, clean intermittent self-catheterization (CISC) is advocated.

A specialist nurse or continence adviser is the most suitable person to instruct the patient, or if necessary their carer, about how to carry out intermittent catheterization. Women find the procedure more difficult initially and often require a mirror to help locate the urethral orifice, but once learnt, even blind or partially sighted patients can become proficient. Many void a variable amount before passing the catheter, but after commencing antimuscarinic medication effective voiding may be so compromised that the patient relies mostly on their intermittent self-catheterization. Frequency of catheterization will best be determined by the patient, but initially they should be advised to perform the procedure three or four times a day, ensuring that the residuals are kept lower than 500 mL. Contact and support by the specialist nurse, particularly in the early stages of learning the technique, increases the patient's confidence and careful follow-up ensures compliance to a prescribed regimen. Asymptomatic bacteriuria is a common finding in those using intermittent self-catheterization and is not an indication for antibiotic treatment.

Catheter technology has advanced significantly in recent years. Various innovative features have been incorporated into the design, although mostly of single-use catheters, with consequent increases in cost. The new catheters are manufactured from different materials, and of differing lengths and diameters. The continence adviser or specialist nurse can advise on the types of catheter available and put the patient in touch with suppliers.

Catheter choice depends on various factors such as ease of use and storage, discomfort and minimization of damage on insertion and the risk of urinary tract infection. Trauma and discomfort are reduced by using gel on the catheter, although many of those that are now available are hydrophilically coated so that on contact with water they develop a highly lubricated surface; some now come packed 'pre-wetted'. Convenience of use has been improved as they are now disposable and can be secreted in pocket or small bag. Those for use in women have been compacted into a tube similar in size to a lipstick container.

Unfortunately, there are few other effective methods for improving bladder emptying. There have been claims that α-blockers can reduce PVR volumes in patients with MS, but the clinical impression is that α-blockers are not effective in individual patients, possibly because incomplete bladder emptying is thought to be the result of a combination of poorly sustained and ill-coordinated detrusor contractions, or of an inappropriate contraction of the striated urethral sphincter.

The application of a suprapubic vibrating stimulus is the only other proven means of improving bladder emptying, and is a method that has benefited some patients. In patients with reflex DO, the vibrating stimulus might help to initiate micturition and possibly improve bladder emptying by triggering a detrusor contraction. Several devices are commercially available for suprapubic vibration, including small hand-held battery-operated vibrators.

First line management of neurogenic incontinence

Complex management and investigation protocols for neurogenic incontinence have been proposed; Figure 24.6 shows a simple algorithm based on the two main interventions directed at the dual problems of DO and incomplete emptying. This has proved to be a convenient low-cost effective management scheme which is in daily use in the authors' department. The role of cystometry and video-cystometry in the investigation of patients with MS has been promoted by some experts because it is only through these investigations that DSD can be diagnosed. However, because there is no definitive treatment for DSD other than by managing the resulting incomplete bladder emptying and raised detrusor pressure, a pragmatic approach does not require these extra investigations.

Other medications

The synthetic antidiuretic hormone desmopressin (DDAVP®) was originally licensed to treat the polyuria of diabetes insipidus but has since been demonstrated to have a useful adjunct role in

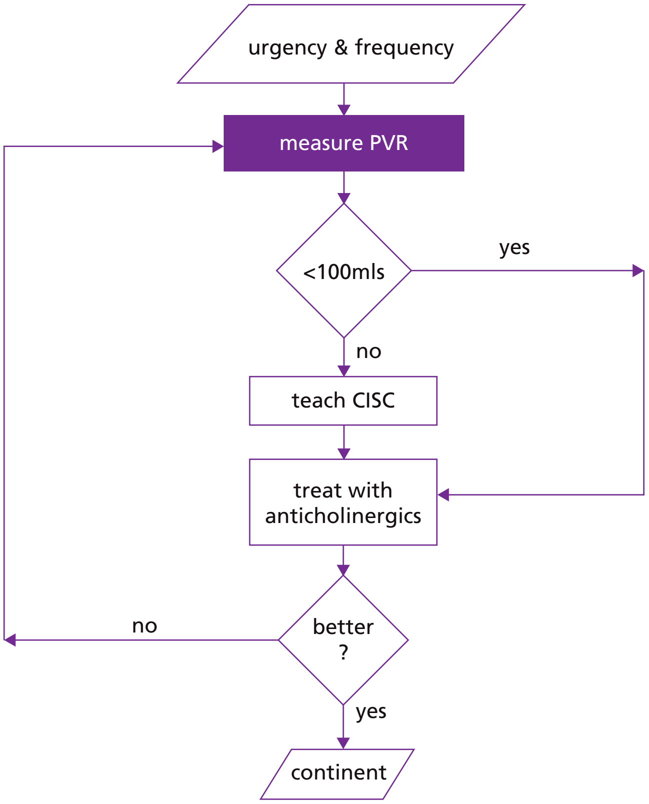

Figure 24.6 Algorithm for management of neurogenic incontinence.

treating patients with neurogenic incontinence. Desmopressin (10–20 μg, by nasal spray) should only be taken once in each 24-hour period, and should not be given to patients over 65 years of age, or used in patients with dependent leg oedema resulting from immobility who have night-time frequency when recumbent. If taken during the day it may provide patients with a period of up to 6 hours untroubled by urinary frequency, without any rebound night-time frequency. In patients with MSA troubled by night-time frequency, it may have the added beneficial effect of ameliorating postural hypotension.

Detrusor injections of botulinum toxin

The most significant recent development in the treatment of neurogenic bladder dysfunction has been the use of botulinum toxin A (BTX-A), injected into multiple sites of the detrusor muscle. The treatment was introduced on the theoretical basis that botulinum toxin would temporarily block the presynaptic release of acetylcholine from the parasympathetic innervated muscles and produce a paralysis of the detrusor smooth muscle, but its clinical effect is so much better than simple bladder paralysis that a more complex action on intrinsic afferent innervation has been hypothesized. Following BTX-A detrusor injections there is an increase in capacity volume at first reflex detrusor contraction and bladder compliance. These urodynamic changes underlie the remarkable symptomatic improvements in reduction of urgency, frequency and incontinence occur, with response rates sometimes approaching 95–100%. Symptomatic improvement occurs early, usually within the first week post injection and lasts for 9–10 months. Data are now becoming available showing that repeat treatments are as efficacious as the first. Amelioration of symptoms is accompanied by significant improvement in patients' quality of life.

Although trials to obtain a licence are currently in progress it is probable that the necessary approvals are still some years away. This is creating difficulties because it is now known that BTX-A treatment could alleviate incontinence of many patients in whom first line measures are no longer effective and, neither bladder surgery nor sacral neuromodulation (see below) are suitable for patients with progressive neurological disease, and no intravesical vanilloid de-afferenting agent such as capsaicin or resiniferatoxin is licensed.

Urinary retention

Although a failure of storage and DO leading to urinary incontinence is the most common bladder disorder seen with neurological disease, failure to empty and urinary retention can also occur, particularly as an acute phenomenon. A review from Japan logically divides the possible neurological causes of acute urinary retention into those caused by central and peripheral nervous systems inflammatory disease (Table 24.3). If the cause is a peripheral lesion there are likely to be signs of herpetic infection, more commonly herpes varicella-zoster virus than herpes simplex. If acute urinary retention is of central origin it may occur in the context of aseptic meningitis, the condition recently described by this same group of authors, the 'meningitis retention syndrome' (MRS). The authors propose that this is a mild form of acute disseminated encephalomyelitis and indeed some of the patients with the syndrome had brisk lower limb reflexes, supporting the hypothesis that the neurology of micturition is particularly sensitive to cord damage.

Other neurological diseases that may cause urinary retention, often chronic retention, have been mentioned in the previous section and summarized in Table 24.4. An important observation for the neurologist is that if the voiding disorder is brought about by a chronic neurological disease, there are almost inevitably other symptoms and signs of that disease. However, if a urologist has referred a man or, more commonly, a young woman with urinary retention and there is no evidence of neurological disease on clinical examination, it is highly unlikely that imaging or other investigations will be abnormal. A diagnosis in these circumstances is often difficult, as described below.

Urinary retention in women

Women with unexplained non-neurogenic urinary retention were, until quite recently, often thought to have a psychogenic cause for their complaint and indeed in modern day practice some women still suffer from this medical misconception. However, in

Table 24.3 Non-progressive inflammatory CNS disease causing urinary retention. After Yamamoto *et al.* (2006).

Disease	Neurological symptoms/signs						Urodynamics	Cerebrospinal fluid (CSF)		MRI	Viral titres
	Headache fever	Stiff neck Kernig	DOC convulsion	LE reflexes	Motor	Sensory	Bladder function	Increased cells, protein	MBP, OCB		
ADEM	+	+	+	N or brisk or decreased	Paraparesis	Sensory level or saddle	DHIC	+	+	WML, brain & spinal cord	no
Meningitis-retention syndrome	+	+	–	N or brisk	–	N	DA	+	+/–	–	no
Myelitis	+/–	+/–	–	Brisk	Paraparesis	Sensory level	DHIC	+	+/–	Spinal cord	no
Sacral herpes	–	–	–	N or decrease	–	Unilateral saddle, skin erruption	DA	+	–	–	VZV, HSV
Equivocal cases*	–	–	–	N	–	N	DA	+	?	–	HSV or no

ADEM, acute disseminated encephalomyelitis; DA, detrusor areflexia; DHIC, detrusor hyperreflexia with impaired contractile function (see text); DOC, disturbance of consciousness; HSV, herpes simplex virus; LE, lower extremities; MBP, myelin basic protein; N, normal; OCB, oligoclonal band; Saddle, sensory disturbance in the saddle/sacral area; Sensory level, sensory disturbance below the cervical/thoracic level; VZV, varicella-zoster virus; WML, white matter lesion.

* Equivocal cases: urinary retention with CSF abnormality alone (see text).

Table 24.4 Neurological causes of complete urinary retention.

	Underlying cause	Accompanying neurological symptoms and signs
Acute neurological condition	Inflammatory nervous system disease (see Table 24.3)	Yes
	Acute spinal disease or injury	Yes
	Sacral root lesion	Yes
	Guillain–Barré syndrome	Yes
Chronic neurological condition	Cortical pathology (very rare)	?
	Brainstem lesion (rare)	Yes
	MS or other cause of chronic spinal dysfunction	Yes
	Multiple system atrophy	Usually
	Cauda equina syndrome	Yes
	Small fibre peripheral neuropathy	Yes
Urological conditions	Post female urethral surgery for incontinence structural causes – excluded by referring urologist	No
Isolated urinary retention in young women	Chronic opioid abuse Association with other enteric myopathy or neuropathy (CIPO) Fowler's syndrome	No

CIPO, chronic intestinal pseudo-obstruction; MS, multiple sclerosis.

1985 an EMG abnormality of the striated urethral sphincter was described which, it was hypothesized, impairs urethral relaxation resulting in obstructed voiding and incomplete retention or complete retention. It was observed that many of the young women also had a history or clinical features of polycystic ovaries and over the last 20 years this condition has since become known as 'Fowler's syndrome'. Although an association with polycystic ovaries is often found this is not essential for the diagnosis, whereas exclusion of underlying urological or neurological pathology is. A retrospective questionnaire survey showed that the syndrome is characterized by painless urinary retention, with a bladder capacity in excess of 1 L, and often difficulty in removing any catheter used for self-catheterization. Anecdotally, many of these women have had a clinical incident that triggered the onset of their symptoms, such as a surgical procedure under general anaesthesia, a urinary tract infection or childbirth. The pathophysiology remains to be fully elucidated but it has been postulated that the disorder is brought about by a hormonally sensitive channelopathy of the striated urethral sphincter causing the muscle to be in a state of involuntary continuous contraction. The constant contraction of the sphincter has an inhibitory effect on the detrusor. Although sphincter EMG is still used to confirm the diagnosis if there is uncertainty, the demonstration of a raised resting urethral pressure and an increased sphincter volume on ultrasound, taken in conjunction with a typical history, are often sufficient for a diagnosis to be made.

The mainstay of treatment had been indefinite intermittent or in-dwelling catheterization but sacral nerve stimulation (SNS) or sacral neuromodulation (SNM) has been shown to restore voiding in these women, probably by resetting brainstem function. SNM was first described as a treatment for urinary retention in the mid-1990s. At the time, SNM had been introduced for the management of bladder dysfunction, paradoxically for both intractable incontinence and retention. The first stage of SNM was an initial test procedure, known as a percutaneous nerve evaluation test (PNE) which, if found to be positive and restore voiding ability, was followed by the implantation of a permanent sacral electrode. Success rates for women with retention for this method were reported at 40–50% for the PNE, with approximately 60% voiding to completion with formal implantation. At Queen Square our experience has been comparable, with two-thirds of patients continuing to void without need for catheterization at 5-year follow-up.

A retrospective study of 247 women referred to the Uro-Neurology department at Queen Square with urinary retention over a 4-year period showed that Fowler's syndrome is the most common diagnosis although this accounts for only 58%. In 32% no diagnosis could be made, but in 2% there was a history of chronic opiate ingestion. There is urodynamic evidence that opioids result in decrease bladder sensation and increase residual volume, as well as decreasing detrusor contractions; animal studies suggest that the activation of mu opioid receptors in the PAG inhibits detrusor contractions. Theoretically, voiding dysfunction should be reversible with reduction and withdrawal of the opioid but we have not been able to show this. In 3% of the patients there appeared to be a relationship with chronic intestinal pseudo-obstruction (CIPO), a rare disorder characterized by severe and chronic constipation without any demonstrable anatomical or mechanical lesion but thought to be caused by a visceral neuropathy or myopathy, usually in infants or children.

There is also an uncommon condition in men where painless urinary retention is not associated with constipation, and sexual function is preserved, but in whom extensive investigation fails to reveal any underlying abnormality. It has been speculated that this disorder is caused by some abnormality of the intrinsic afferent innervation, possibly loss of the recently described 'myofibroblast' or interstitial cell, thought to be an integral part of the bladder stretch sensing mechanism, although no proof exists at the present time. Presumably this same condition makes up a proportion of the women with unexplained urinary retention.

Sexual function and its neurological control

Physiology

Human sexual function depends on integrity of the nervous system at many levels: higher centres determine the cognitive and emotional aspects of sexuality, hormonal levels drive libido and desire through the hypothalamus, and the ability to effect a sexual response depends on spinal autonomic reflexes. Malfunction of some aspect of this highly distributed system is therefore common in neurological disease.

Functional imaging techniques have been applied to examine brain responses on sexual arousal and Figure 24.7 is a metanalysis of four studies that used erotic visual stimulation compared with erotically neutral viewing in healthy subjects of both genders. Activation of the prefrontal cortex, the anterior cingulate, occipito-temporal cortex, thalamus, amygdala, hypothalamus, insula and claustrum is seen, those regions being part of the limbic and paralimbic system long known to be important in mediating sexual motivation. The hypothalamus has been linked

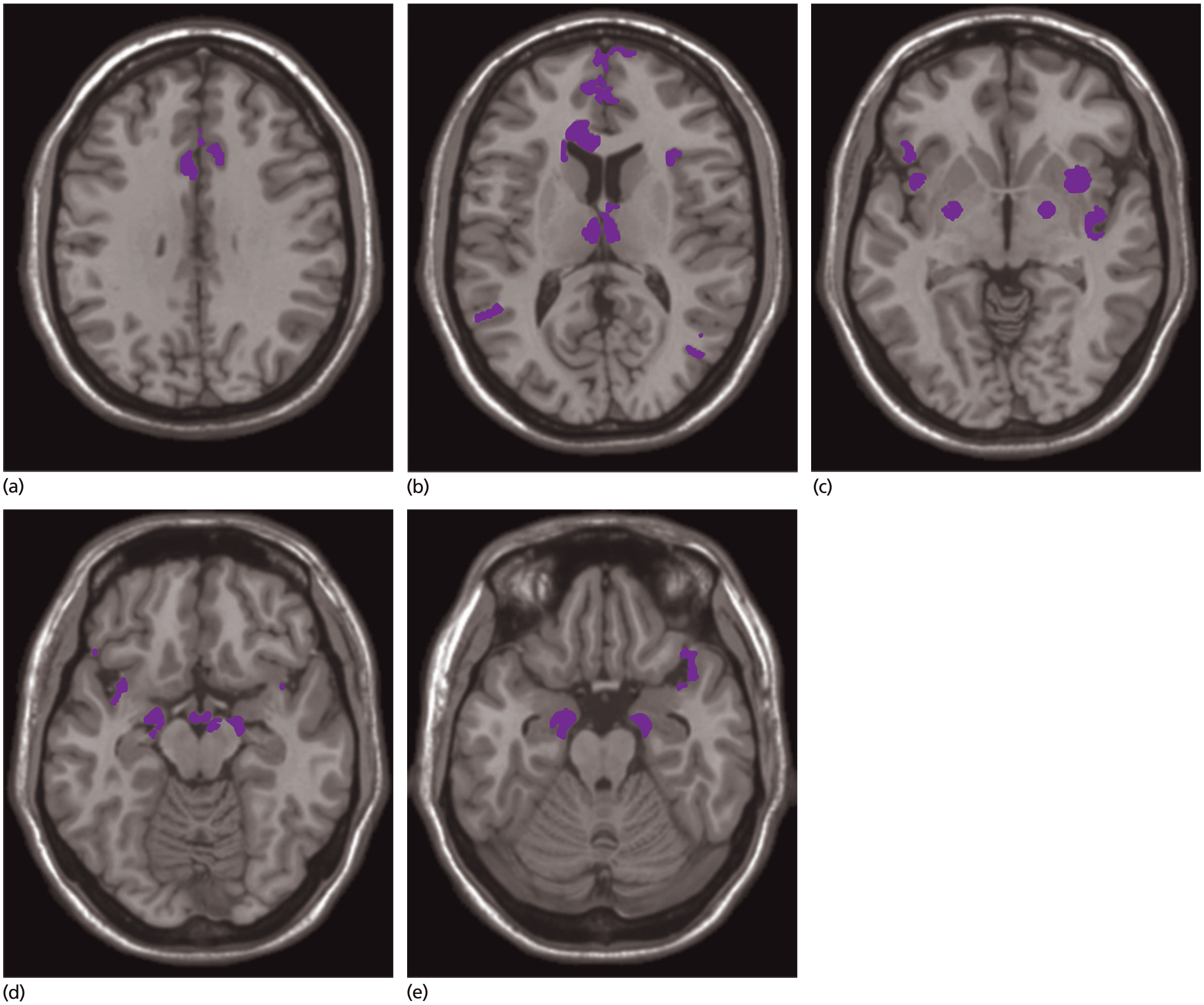

Figure 24.7 Metanalysis of functional magnetic resonance studies that showed responses to erotic visual stimulation.

to most aspects of sexual behaviour in both humans and animals. A study of brain activation during penile stimulation by the subjects' females partners showed strong activation predominantly on the right side of the insula and secondary somato-sensory cortex and de-activation of the amygdala but no activation of the hypothalamus. The same group reported brain activation during male ejaculation and showed prominent activity in the dopamine rich mesodiencephalic junction/ventral tegmentum, an area that was also seen to be activated with the 'rush' experienced by heroin and cocaine addicts who describe an orgasmic-like sensation with heroin use.

Animal and human studies following spinal cord injury have pointed to the existence of two independent pathways for the male erectile response: a psychogenic pathway mediated by the thoraco-lumbar sympathetic outflow (T12–L2) and a sacral spinal reflex pathway, whereby genital stimulation results in a short-lived erection. In neurological health these two responses appear to fuse to produce an erection adequate for intercourse. Comparable pathways mediate vaginal lubrication, the female sexual response analogous to penile erection.

Erection results from increased blood flow into the corpus cavernosum, a response mediated by the efferent parasympathetic pathway originating in the intermediolateral aspect of the sacral cord (S2–S4) travelling in the pelvic nerve (nervi erigentes). The preganglionic neurotransmitter in these fibres is acetylcholine but the post-ganglionic nerve fibres which terminate either on the vascular smooth muscle of the corporeal arterioles on the non-vascular smooth muscle of trabecular tissue surrounding the corporeal lacunae release nitric oxide (NO).

In women, sexual arousal results in an increased vaginal blood flow, erection of the cavernous tissue of the clitoris and the outer part of the vagina. As in men, the erectile response of these tissues is NO dependent; neuronal NO synthetase has been detected in both the body and glans of the clitoris. Nerve fibres containing vasoactive intestinal polypeptide (VIP), calcitonin gene-related peptide (CGRP) and substance P (SP) have also been described in human clitoral tissue. Normal vaginal lubrication, which is dependent both on intact innervation and normal oestrogen levels, is also NO mediated.

Detumescence after orgasm is mediated by noradrenaline in the sympathetic system and in the absence of sexual arousal it maintains the penis in the flaccid state. In men, orgasm and ejaculation are not the same process. Ejaculation involves emission of semen from the vas and seminal vesicles into the posterior urethra, and closure of the bladder neck, under sympathetic control, whereas orgasm involves contraction of the pelvic floor muscles under somatic nerve control from the perineal branch of the pudendal nerve. In neurological disease the two processes can be separately affected.

During female orgasm there may be a series of synchronous contractions of the sphincter and vaginal muscles, with associated sensory changes which are generally described as being intensely pleasurable pelvic events.

Sexual dysfunction: prevalence

Various classifications of sexual dysfunction have been proposed, the most recent being one that included categories of hypoactive sexual desire, or disorders of sexual arousal, orgasms or sexual pain. Many of these disorders are common amongst the general population: the Male Massachusetts study showed an increasing prevalence of erectile dysfunction (ED) with age so that of a group of men aged 60–70 almost 60% had ED to a greater or lesser extent. The prevalence of female sexual dysfunction (FSD) has been estimated to be 25–63%, the figure depending on the definition used and populations studied. Amongst groups of patients with neurological disease the prevalence of all types of disorder is even higher, although precise figures are not known.

Neurological causes of sexual dysfunction

Cortical disease

Cortical problems following traumatic brain injury, encephalitis, stroke and pathologies that cause epilepsy affecting the temporal or frontal regions can result in sexual disturbances.

Traumatic brain injury

Sexual dysfunction, usually reduced sexual desire, is common following traumatic brain injury particularly if there has been substantial cognitive damage. Both the amount of brain tissue and the location determine the outcome. Damage to prefrontal areas can result either in erotic apathy or conversely disinhibition with inappropriate sexually demanding behaviour. Similar problems can be seen following encephalitis. Partner dissatisfaction plays an important part in influencing sexual activity following traumatic brain injury.

The importance of hypothalamic and pituitary damage following head injury and resulting hypopituitarism has recently been recognized, and full endocrine evaluation some months after a significant brain injury is sometimes appropriate.

Stroke

Although pre-existing sexual dysfunction resulting from diseases such as hypertension, diabetes and myocardial infarction may mean that there is less impact of stroke on sexual behaviour, the frequency and spectrum of sexual problems can be comparable to those seen following traumatic brain injury.

Epilepsy

Temporal lobe disease causing epilepsy is particularly likely to have sexual manifestations. Sexual auras can occur as part of complex partial seizures and genital automatisms were observed in 11% of patients undergoing diagnostic video-telemetry.

Although various sexual perversions and occasionally hypersexuality have been described in patients with temporal lobe epilepsy (TLE), the picture most commonly seen is that of a profound failure of arousal.

There is sufficient evidence from studies that have compared sexual dysfunction in patients with generalized epilepsy and those with TLE to suggest that the deficit is a result of a specific temporo-limbic involvement rather than a consequence of epilepsy, psychosocial factors or antiepileptic medication. The problem is usually that of a low or even absent libido – something that may be a presenting complaint either because of its effect on sexual relationships formed prior to the onset of the disorder or because lack of sexual motivation prevents the formation of adult relationships. In a study that looked at changes in sexuality following epilepsy surgery, extra-temporal resections usually resulted in no change whereas temporal lobe resection resulted more commonly in a change in sexuality. In one study, patients who reported a postoperative sexual increase had a significantly larger amygdala volume contralateral to the site of their resection surgery than patients with a sexual decrease or no change. These observations were interpreted as providing evidence for an important role of the amygdala in regulating human sexual function and behaviour.

Parkinson's disease

Whether or not specific genital dysfunction is a feature of PD is not entirely resolved. Using questionnaire surveys, several studies have shown that dissatisfaction with the quality of sexual experiences in men with PD in more likely than in control subjects. A survey of young patients with PD and their partners revealed a high level of dissatisfaction, with the most severely affected couples being those in which the patient was male and who complained of ED and premature ejaculation. Although ED, premature ejaculation in men and difficulty in arousal and reaching orgasm in women with PD may be significant problems, unless age and disability matched groups are compared it is difficult to know how specific these complaints are to PD. Early studies that found a high incidence of ED in men with PD may not have excluded men with MSA. A study that compared a group of married men with PD with a group with arthritis found a similar pattern of sexual functioning in the two groups, but suggested that although sexual dysfunction was common in PD, it was not more so than in men with a chronic illness that does not involve the nervous system. Age, severity of disease and depression, as well as testosterone levels, seem to be major determinants of sexual dysfunction, as they are in other neurological diseases.

The role of dopamine in reward-seeking behaviour, gambling addiction and hypersexuality is complex. There is experimental and human evidence that dopaminergic mechanisms are involved both in determining libido and inducing penile erection. In animal studies the medial preoptic area of the hypothalamus has been shown to regulate sexual drive and selective stimulation of D2 dopaminergic receptors in this region increases sexual activity in rats. An increase in libido in some patients with PD treated with levodopa is a well-observed problem, although the extent to which this occurs is uncertain. There is an element of dose dependency between antiparkinsonian drugs and hypersexual behaviour and it has been described after the introduction of pergolide and also following deep brain stimulation.

The pro-erectile effect of sublingual apomorphine was exploited as a licensed worldwide treatment for erectile dysfunction in 2001. Although some men with PD being treated with apomorphine had been taking advantage of this effect, no large-scale study of its effect in men with PD or MSA was carried out and since its licensing other therapies have been shown to be more effective.

Men with PD respond satisfactorily to treatment with sildenafil citrate and recently a small but positive response in sexual well-being was reported in men, but not women, after deep brain stimulation of the subthalamic nucleus.

Multiple system atrophy

Erectile dysfunction may be a prodromal symptom of MSA. Initially, erectile response becomes intermittent and over the course of months or years erectile failure becomes complete. This can certainly pre-date the onset of recognized neurological features by several years. This was previously thought to be part of the symptom complex of autonomic failure, but the occurrence of this complaint is clearly separate from postural hypotension; it has been speculated that there is some more central, possibly dopamine-dependent, underlying process. Initially, libido remains intact and men treated with phosphodiesterase inhibitors who already have postural hypotension appear to be at particular risk of exacerbation. It is not clear whether ejaculation is equally affected and little information exists about whether or not sexual function in women is equally seriously disrupted.

Spinal cord injury

The earliest reports of human neurogenic sexual dysfunction were by Bors and Comarr in large series of war veterans who had sustained spinal cord injury. These early studies showed that the level and completeness of a lesion determined the extent of preserved erectile and ejaculatory capacity of a paraplegic man and it was from these observations that the concept of there being both spinal reflex and psychogenic pathways for erection originated. Following a complete cervical lesion, psychogenic erections were lost but spontaneous or reflex erections remained intact. In low lesions, particularly if the cauda equina was involved, there was poor or absent erectile capacity. Because the thoraco-lumbar sympathetic outflow originates between T12 and L2 and it is through this pathway that psychogenic erectile responses are mediated. Occasionally men with low lumbar cord lesions but intact sacral roots find that they are still able to obtain psychogenically driven erectile responses.

Ejaculation also depends on spinal cord integrity and from studies of men who have undergone bilateral anterolateral cordotomies for relief of pain and lost orgasmic sensation, it is known that 'erotically coloured' sensation is conveyed in spinal pathways which travel in close proximity to the spinothalamic tracts. Anorgasmia has been described following an anterior cord syndrome where patients have been demonstrated to have loss of small myelinated nerve fibre function while large fibre dorsal column functions were spared. Preserved ejaculation function following a spinal cord lesion is unusual and it was found that only 4% of men following spinal cord injury were still able to ejaculate, a matter of the greatest concern to paraplegic young men who wish to father children.

Much less is known about sexual dysfunction in women with spinal cord injury but it seems that all aspects of genital neurology are affected; the women have little or no genital sensation, experience poor vaginal lubrication and have difficulty in reaching orgasm. As with erectile function in men, the analogous process of vaginal lubrication appears in health to be determined by psychogenic and reflex pathways and thus the level and completeness of a spinal cord injury determines what responses are preserved. A sensory level above T11–L2, the segmental origin of the thoracolumbar sympathetic outflow, was found to be associated with a failure to achieve psychogenic lubrication. By contrast, reflex genital vasocongestion in response to manual stimulation occurred despite a lack of subjective arousal, whereas women with cauda equina damage cannot usually achieve reflex lubrication. In women with preservation of sensory function in T11–L2, the psychogenic genital vasocongestion response is maintained. This suggests that the sympathetic outflow in the female is as important as it is in the male. Women with complete or incomplete suprasacral injury can achieve reflex genital response by manual stimulation but not when there is involvement of the sacral roots. Failure to reach orgasm is common in women with spinal cord injury and correlates poorly with the type of injury. Although their ability to reach orgasm is diminished, the written descriptions of the experience of orgasm in women with spinal cord injury were indistinguishable from those of able-bodied women, although they took much longer to achieve orgasm. It has been hypothesized that this preserved responsiveness is mediated through intact vagal innervation of the cervix.

Multiple sclerosis

The evidence points to spinal cord involvement as the major cause of erectile dysfunction (ED) in MS. Cord involvement in MS may initially result in a partial deficit so that ED is variable, with preserved nocturnal penile erections and erections on morning waking. It is only in the last 10–20 years that neurological teaching has recognized the error of the dictum that ‘if a man can get an erection at any time, impotence is likely to be psychogenic’. The experience of men with spinal cord injury obviously belied that statement, but early studies put the incidence of ‘organic impotence’ in men with MS as low as 4%. Now it known to be a common problem, with estimates that it affects 50–75% of men with MS, depending on the severity of disability of the group studied.

A study that analysed the type of sexual dysfunction which affected men with MS who were still ambulant found that erectile dysfunction was the most common complaint (63%), followed by ejaculatory dysfunction and/or orgasmic dysfunction (50%) and reduced libido (40%). Other non-specific effects of MS may also have adverse effects on sexual function, including fatigue, depression, spasticity and anxiety about incontinence.

Prior to the advent of the oral erectogenic medications, men with MS were being successfully treated with intracavernosal injection therapy. Subsequently, a multicentre placebo controlled trial demonstrated an excellent response to sildenafil citrate by men with MS. Orgasmic capacity was also increased, a fact that was attributed to the men being able to sustain an erection for longer. Although many men are helped through that mechanism, a significant number continue to have difficulty with ejaculation for which there is no effective medication, although yohimbine may be tried. Probably the best recourse is to a vibrating sex aid.

Women with MS appear to report sexual dysfunction less frequently than men, but nevertheless it is a problem that is thought to affect more than 50%, the incidence increasing with increasing disability. Although a recent US questionnaire survey of 133 women with mild disability found that although half reported voiding symptoms, 70% still enjoyed sexual intercourse, felt aroused and could experience orgasm. These figures are consistent with other questionnaire surveys that show that approximately one-third of women with MS experience loss of orgasm, reduced libido or decreased lubrication. Sensory dysfunction in the genital area was experienced by 62% of women with advanced MS. The nature of the sensory dysfunction is usually loss of sensation but occasionally, particularly early in the course of the disease, dysaesthesia can make genital contact with their partner unbearable. Loss of orgasmic capacity is the complaint for which women seek treatment. Following the acknowledged success of sildenafil citrate in the treatment of sexual function with men with MS, 19 women were recruited to a double-blind placebo controlled trial. A questionnaire was used to measure sexual response and although there was a significant improvement in the lubrication and some improvement in sensation, there was no overall change in orgasmic response to sildenafil compared to placebo. The responses to the ‘global efficacy question’ reflect limited overall subjective improvement following sildenafil. This was disappointing although perhaps not surprising. Despite the absence of specific treatment, the opportunity to discuss their problem with a health care professional was found to be beneficial to these women.

Sympathetic thoraco-lumbar outflow lesions

The fibres that travel from the thoraco-lumbar sympathetic emerge from spinal levels T10–L2 and course through the retroperitoneal space to the bifurcation of the aorta, from where they enter the pelvic plexus. Loss of sympathetic innervation of the genitalia causes disorders of ejaculation with either failure of emission or retrograde ejaculation, although the ability to experience the sensation of orgasm may be retained. The sympathetic thoraco-lumbar fibres are particularly likely to be injured by the procedure of retro-peritoneal lymph node dissection and complaints of loss of ejaculation are common after such surgery.

Conus or cauda equina lesions

The cauda equina contains the sacral parasympathetic outflow together with the somatic efferent and afferent fibres. A lesion of the cauda equina therefore results in sensory loss as well as a parasympathetic defect and following such a lesion both men and women complain of perineal sensory loss and loss of erotic genital sensation – for which there is no effective treatment. In men erectile dysfunction is also a complaint.

A recent detailed study of 36 men with long-standing cauda equina damage of various aetiologies used a self-administered questionnaire to gauge sexual dysfunction and found severe dysfunction in 35%, moderate in 24% and slight sexual dysfunction in the remainder, with only one man highly confident of achieving and maintaining an erection. Orgasmic function was slightly more impaired than erectile function and sexual desire slightly less. The patients' age, but not findings on clinical neurological, even perineal sensation or EMG of the anal sphincter, correlated with sexual dysfunction. There had been very little recovery of function since onset and only five men had received medical attention for their problem.

Peripheral neuropathy

Diabetes is the most common cause of erectile dysfunction. Surveys of andrology clinics have found 20–31% of men attending to be diabetic. The prevalence of erectile dysfunction increases with age and duration of diabetes and the problem is known to be associated with severe retinopathy, a history of peripheral neuropathy, amputation, cardiovascular disease, raised glycosylated haemoglobin, use of antihypertensives and higher body mass index. A large population study of men with younger onset diabetes found 20% to have erectile dysfunction. Whether the pathogenesis of erectile dysfunction in diabetics is caused mainly by neuropathy or whether there is a significant micro-vascular contribution or the two processes are co-dependent is not yet resolved, but at a cellular level the evidence suggests there is a depletion of neurotransmitters. Age-matched studies of women with and without diabetes suggest that diabetic women may also be affected by specific disorders of sexual function including decreased vaginal lubrication and capacity for orgasm.

Guillain–Barré syndrome (GBS) does not appear specifically to affect the innervation involved in sexual function over and above the extent to which it causes general disability. In about 25% bladder symptoms appear after onset of weakness, but it is unknown if these are the patients who on recovery are likely to have sexual dysfunction. GBS patient support groups report anecdotally of sexual dysfunction in both genders as part of general disability.

By contrast, neuropathies that involve selectively the small and unmyelinated nerve fibres, such as amyloid and some other rare inherited neuropathies, have uro-genital symptoms as prominent features. Amyloid neuropathy, either familial or secondary, has a marked effect on uro-genital function and symptoms are common amongst the complaints of patients. Erectile dysfunction may be an early symptom of autonomic involvement.

Management of sexual dysfunction

Measures such as pelvic floor exercises or electrical stimulation feedback with cognitive therapy, which may improve symptoms in the neurologically intact, have not been found to be as effective in those with neurogenic sexual dysfunction. In men with neurogenic erectile dysfunction, corporeal injections of first papaverine and then alprostadil were the mainstay of treatment until the advent of sildenafil citrate, the Type 5 phosphodiesterase inhibitor (PDE-5) in 1998.

Normal erectile function is dependent on the smooth-muscle relaxing effects of NO which is mediated by the cyclic nucleotide signalling pathway. Down-regulation of this pathway is central to the pathophysiology of many forms of erectile dysfunction. Hence, selective inhibition of PDE-5 that catalyses the degradation of cyclic guanosine monophosphate (cGMP), promotes erectile responses to sexual stimulation. The efficacy of sildenafil citrate transformed the treatment of erectile dysfunction, not only by providing an effective well-tolerated oral therapy, but also by introducing open discussion about the problem. The recent advent of vardenafil, which has the highest *in vitro* potency, may improve responsiveness, and tadalafil, which has a prolonged half-life of 18 hours, is enabling couples to have sexual activity with less planning.

Female sexual dysfunction is less satisfactorily treated. Erectile dysfunction will affect the female partner, and in an ideal world it is recommended that evaluation of the woman should be addressed within the context of the couple in a sexual medicine clinic. Although the pharmaceutical industry has been criticized for 'disease mongering', inventing the condition of female sexual dysfunction to promote drug sales, genuine neurogenic female sexual dysfunction is unfortunately a reality for which there is at present no specific treatment. However, it may be worthwhile considering the treatable general aspects of pelvic floor dysfunction, as a consequence of childbirth and the importance of the menopause in the older woman. Hormone replacement therapy has been used extensively and effectively, if libido is affected greatly; the use of testosterone products has also been reported to be valuable.

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25 Systemic Conditions and Neurology

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Neurology has developed somewhat separately from the body of general medicine. However, the subjects remain inextricably linked, because diseases of all body systems can profoundly influence the nervous system. About 1 in 5 acute medical admissions to district general hospitals in the UK are due to neurological illness. General physicians often lack first hand experience in managing patients with neurological symptoms; neurologists can make important contributions to optimizing management, often assisting with accurate diagnosis, appropriate investigation and treatment. Effective communication between neurologists and general physicians is thus critical.

In this context, a working knowledge of the neurological aspects of general medical conditions is invaluable and this chapter aims to summarize neurological manifestations of disorders of other body systems, outlining some basic elements of pathophysiology, diagnosis and management. It is intended neither to be exhaustive, nor a comprehensive and detailed guide to treatment. Rather, we aim to give a broad overview of the range of neurological disease encountered in general medicine. The all-important management of systemic hypertension is dealt with in Chapter 4 and the disabling effects of hypotension in Chapter 23. Issues relating to epilepsy in women of the childbearing age and pregnancy are also discussed here.

Cardiovascular disorders

The neurological consequences of cardiovascular disease are common and often devastating. Ischaemic stroke and transient ischaemic attack (TIA) – the main clinical result of embolism from the heart or great vessels – are briefly considered here but also dealt with in detail in Chapter 4. An understanding of the effects of vascular disease of the great vessels and spinal cord requires an understanding of basic vascular anatomy, outlined here.

Neurological consequences of aortic pathology

Anatomy

The whole body, including the nervous system, is supplied by the aorta. Disease processes affecting the aorta and surgical instrumentation can therefore cause damage to the brain, spinal cord and peripheral nervous system. The neurological syndrome caused depends more on the part of the aorta affected, rather than the nature of the pathology.

Blood supply

Cerebral

The aorta leaves the heart to become the aortic arch; the great vessels supply the brain, brainstem and cervical spinal cord (Figure 25.1). From the heart, the order in which these vessels arise is as follows: innominate (brachiocephalic) artery – continuing as the right subclavian artery and giving rise to the right common carotid; then the left common carotid, and finally the left subclavian artery. Each vertebral artery arises from the subclavian of that side.

Spinal

The anterior spinal artery is formed from paired branches arising from the vertebral arteries which descend at the level of the medulla. The anterior spinal artery is joined by radiculomedullary arteries at various segmental levels. The mid-thoracic anterior spinal artery is generally supplied by a small feeding vessel. The anterior spinal artery at the level of the lumbar enlargement is supplied by a single large vessel, the great anterior medullary artery of Adamkiewicz (Albert Adamkiewicz, 1850–1921, Professor of General and Experimental Pathology, Cracow). This artery usually runs alongside a nerve root on the left side, usually between T9 to L2. The posterior spinal arteries are also formed from the intracranial vertebral arteries rostrally but after their origin become mixed with a posterior pial arterial plexus

Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

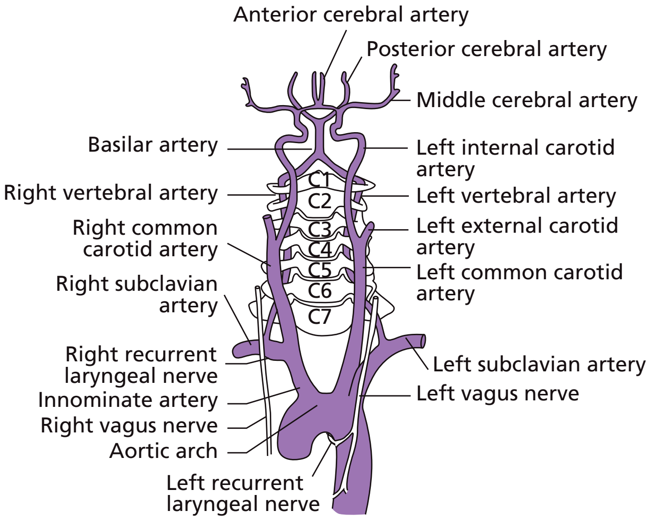
Anterior cerebral artery
Posterior cerebral artery
Middle cerebral artery
Basilar artery
Left internal carotid artery
Right vertebral artery
Left vertebral artery
Right common carotid artery
Left external carotid artery
Left common carotid artery
Right subclavian artery
Right recurrent laryngeal nerve
Left subclavian artery
Innominate artery
Left vagus nerve
Right vagus nerve
Aortic arch
Left recurrent laryngeal nerve
C1
C2
C3
C4
C5
C6
C7

Figure 25.1 Vessels arising from the aorta. From Goodin (1992) with permission.

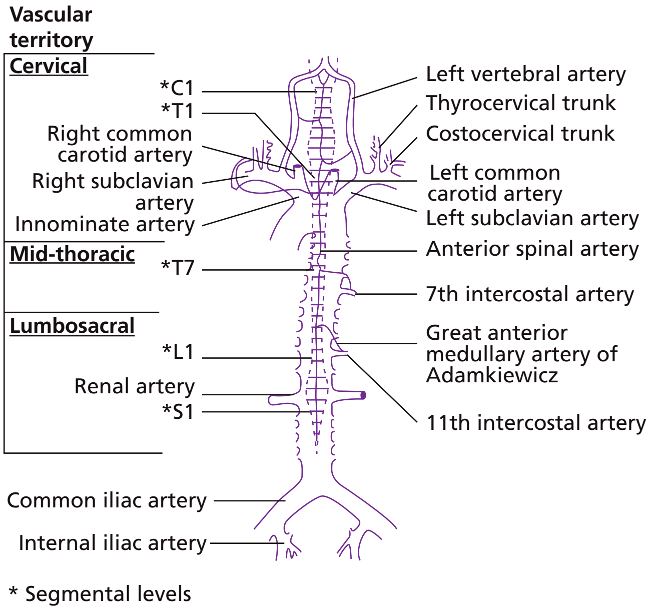
Vascular territory
Cervical
*C1
*T1
Right common carotid artery
Right subclavian artery
Innominate artery
Mid-thoracic
*T7
Lumbosacral
*L1
Renal artery
*S1
Common iliac artery
Internal iliac artery
* Segmental levels
Left vertebral artery
Thyrocervical trunk
Costocervical trunk
Left common carotid artery
Left subclavian artery
Anterior spinal artery
7th intercostal artery
Great anterior medullary artery of Adamkiewicz
11th intercostal artery

Figure 25.2 Blood supply of the spinal cord. From Goodin (1992) with permission.

joined at various levels by posterior radiculo-medullary vessels (Figure 25.2).

Cerebral ischaemia resulting from aortic disease

Aortic disease, such as atherosclerosis, aortitis or aneurysm, can cause cerebral ischaemia, i.e. stroke, TIA and hypoperfusion syndromes. Aortic atheroma is an increasingly recognized source of embolic material to the brain and, although difficult to detect by non-invasive imaging, it can be well visualized by trans-oesophageal echocardiography. Neurological syndromes caused by aortic disease are often indistinguishable from those produced by emboli from other sources.

Steal syndromes can result from occlusive disease of the innominate or subclavian vessels proximal to the origin of a vertebral artery. The left side is three times more likely to be affected than the right, probably because the different vertebral–subclavian angle compared with the right predisposes to atheroma. The word steal describes reverse flow, usually in a vertebral artery, typically exacerbated by exercising the ipsilateral arm, thus increasing blood flow to the arm and metabolic demand or, less commonly, neck movement. Non-invasive imaging of these phenomena suggests that in the vast majority of cases such a steal is asymptomatic, but surgical or endovascular intervention may be considered if symptoms are troublesome. The term subclavian steal syndrome should only be used if symptoms are present; these are usually of posterior circulation ischaemia including vertigo, visual disturbances and ataxia.

Spinal cord ischaemia resulting from aortic disease

The most common spinal cord ischaemic lesion is an anterior spinal artery syndrome, characterized by loss of spinothalamic sensation (pain and temperature), paralysis (usually bilateral) below the level of the lesion with preserved dorsal column function (vibration and joint position) and loss of sphincter control. This may develop abruptly or evolve over several hours. Clinically, at the onset radicular thoracic pain occurs and is often severe. The cervical spinal cord has a more robust vascular supply than the thoracic and lumbar regions, from collateral feeders so that cervical cord infarction is uncommon. Very rarely, dissection of the extracranial vertebral arteries can cause cervical cord ischaemia with brachial diplegia and neck pain. The mid to lower thoracic region is selectively vulnerable to ischaemia, and this is the authors' experience, although not confirmed in all studies. Atherosclerosis and thromboembolism in the anterior spinal artery is rare; infarction in this territory is often a result of aortic disease or surgery. However, no cause is identified in more than 50% of cases. The diagnosis of spinal infarction is clinical, but magnetic resonance imaging (MRI) shows signal abnormalities in the cord in the majority (Figure 25.3). Diseases of the aorta including atherosclerotic occlusive disease, aortitis, dissection, aneurysms or coarctation can all cause spinal cord ischaemia. In order to produce cord ischaemia, the pathological process generally must involve the suprarenal aorta, because the most important radiculomedullary arteries that feed the cord usually originate above this level.

Although the spinal cord syndrome caused will generally be similar regardless of the underlying pathology, dissection of the thoracic aorta presents classically with searing interscapular pain, shock and asymmetric arm pulses. The dissection commonly causes ischaemia of the mid-thoracic spinal cord, producing a thoracic sensory level. Cardiac or aortic surgery requiring clamping of the aorta for over half an hour, and aortic angiography can also cause an anterior spinal artery syndrome. The likelihood of spinal infarction is up to 1 in 10 following a surgical procedure involving the suprarenal aorta, but is rare following infrarenal procedures. In some post-instrumentation cases the mechanism

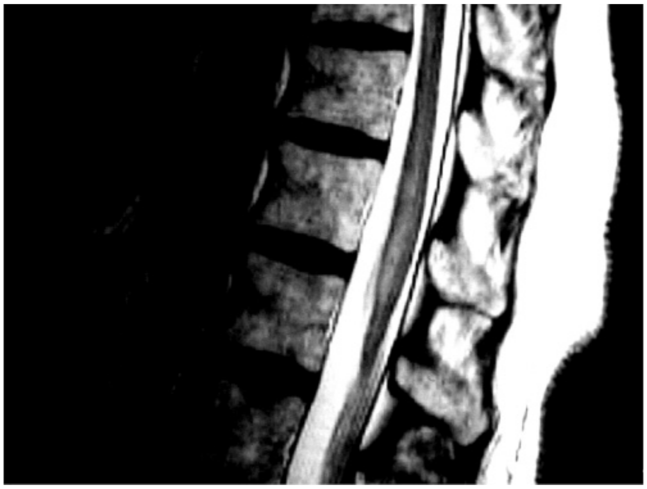

Figure 25.3 Spinal cord infarction. A 60-year-old woman presented with sudden radicular low back pain radiating around the umbilicus with sudden leg weakness and numbness. This progressed over several hours with loss of sphincter function. T2 coronal MRI shows abnormal high signal in the central portion of the lower dorsal cord.

may be a cholesterol embolus arising from an atheromatous aorta. Inflammation of the aorta can cause neurological symptoms directly or indirectly via the development of aneurysms, aortic stenosis or atherosclerosis.

Syphilitic aortitis was common prior to the introduction of penicillin but is now rare. It typically affects the thoracic aorta, causing aneurysmal dilatation and cerebral embolism. Atherosclerosis, by contrast, causes aneurysmal dilatation of the abdominal aorta. Takayasu's disease is a large vessel vasculitis that can cause aortitis, typically in female patients under 30 years of age. This rare condition has a pre-pulseless phase with systemic symptoms of fever, weight loss, arthralgia, myalgia, night sweats and chest pain. This develops into the pulseless phase, in which there is occlusion of the major vessels of the aortic arch with aortic regurgitation, aneurysm formation and hypertension. Cerebral ischaemia is uncommon.

Neurological complications of cardiac surgery

Cardiac surgery, particularly coronary artery bypass grafting (CABG) is one of the most common thoracic operations performed in developed countries. Early neurological sequelae include acute stroke (1–5% of patients), delirium and confusion. Later on, an encephalopathy may become apparent. The mechanisms underlying these complications include particulate microemboli and hypoperfusion during surgery and postoperative atrial fibrillation. Embolism is the most common mechanism of postoperative stroke, accounting for some 60% of cases. Pre-existing symptomatic cerebrovascular disease is a strong risk factor for postoperative stroke. Carotid stenosis (asymptomatic or symptomatic) may be identified, leading to the question of intervention. Although carotid stenosis is associated with an increased risk of postoperative stroke, studies show that in most cases it is not directly causal; it is likely that the stenosis is simply one marker of generalized vascular disease. For this reason the management of asymptomatic carotid stenosis pre-operatively is controversial; randomized trials are needed to guide such management decisions. The available data do not support routine intervention in patients with asymptomatic carotid stenosis, but if the stenosis is high grade (>90% or occlusion) or bilateral, intervention may be considered. Generally, in symptomatic patients with carotid stenosis greater than 70% intervention prior to cardiac surgery is recommended. It is not known whether intervention on the carotid is best performed before or simultaneously with the cardiac surgery; some advocate a joint procedure to avoid two potential peri-operative stroke risks.

Neurological complications of acquired cardiac disease

Cardiac embolism

Ischaemic stroke can be caused by large vessel atherosclerosis and thrombo-embolism, small vessel occlusion, cardiac embolism and miscellaneous rarer causes including arterial dissection, haematological abnormalities and metabolic conditions. Cardiac embolism accounts for up to one-quarter of all ischaemic strokes. Clinical and radiological findings suggestive of cardio-embolism include abrupt and maximal deficit at onset (rather than stepwise) and haemorrhagic transformation (due to rapid reperfusion) or multiple vascular territory infarcts on imaging, with an identified potential cardiac source on echocardiography, and striato-capsular infarction. About 80% of cardiac emboli enter the anterior cerebral vessels; an anterior circulation branch occlusion is highly suggestive of a cardio-embolic source. Although cardio-embolism to the posterior circulation is less common, certain stroke syndromes are characteristic, including the 'top of the basilar syndrome' (reduced conscious level, visual field loss, limb sensory or motor symptoms), and unilateral posterior cerebral artery occlusion causing isolated hemianopia. Of course, none of these features are specific; it must be remembered that a definitive diagnosis of cardiac embolism can be difficult in the presence of coexisting large vessel athero-thrombotic or cerebral small vessel disease. Common sources of cardiac embolism are shown in Table 25.1.

Rhythm disturbances

Atrial fibrillation

Atrial fibrillation (AF) is associated with a sixfold increase in stroke risk. There is a cumulative risk of stroke in patients with AF, which can be stratified according to additional factors. Important factors increasing the stroke risk in patients with AF include age, history of previous stroke, hypertension and left ventricular dysfunction. The presence of one or more of these risk factors should lead to consideration of anticoagulant treatment with warfarin, which reduces the risk of stroke by about 70%. Warfarin has recently been shown to be superior to aspirin in older patients as well as those under 75 years of age.

Sick sinus syndrome

Sick sinus syndrome is defined by sinus node dysfunction, often idiopathic and common in the older population. Patients are

Table 25.1 Common sources of cardiac embolism.

Rhythm disturbances
Atrial fibrillation
Sick sinus syndrome

Cardiomyopathy
Congenital
Acquired – alcohol, recreational drugs (cocaine), amyloid, ischaemic heart disease

Valve disease
Endocarditis
Rheumatic heart disease
Mitral valve prolapse
Prosthetic valves

Structural cardiac lesions
Atrial myxoma
Ventricular aneurysm
Patent foramen ovale
Ventricular akinesia

often asymptomatic, although syncope, palpitations or dizziness may occur. Rhythm disturbances include sinus bradycardia, sinus arrest, sino-atrial block, and bradycardia–tachycardia syndrome. Cardio-embolic stroke occurs in up to 20% of patients, and is more common in those with tachyarrhythmias. Pacemakers do not definitively reduce the risk of stroke. If atrial fibrillation occurs, anticoagulation may be considered to reduce the risk of stroke.

Cardiomyopathies

Primary cardiomyopathies, i.e. not caused by diseases such as ischaemic heart disease, are associated with arrhythmias and a tendency for stasis of blood within the heart, which can lead to left ventricular thrombus formation and embolism to the brain. Dilated or restrictive types are far more likely to be a cause of embolism than hypertrophic cardiomyopathies, in which cerebral embolism is rare. Primary cardiomyopathies have a genetic component, and family screening may be indicated. Anticoagulation may be indicated to prevent recurrent events.

Valve disease

Infective endocarditis is an important cause of embolism to the brain, which occurs in about one-fifth of cases. Usually, emboli occur during active infection, when the patient will usually be systemically unwell with fever, malaise and evidence of emboli to other organs such as the skin, eyes and kidneys. Patient groups at particular risk of endocarditis include those with immunosuppression, intravenous drug use, prosthetic heart valves or structural heart valve disease. Embolic material may cause infection or vasculitis of vessels where emboli impact, with or without the development of a mycotic aneurysm (often in the distal branches of the middle cerebral artery). Any of these processes can cause intracerebral haemorrhage (Figure 25.4). Anticoagulation is not recommended in native valve endocarditis because of the high risk of haemorrhagic complications. However, in the case of prosthetic valve endocarditis anticoagulants may need to be continued, although it is probably safe to discontinue them for 1–2 weeks acutely. Early cerebral angiography is generally advised in the case of areas of symptomatic haemorrhage to exclude mycotic aneurysm, which can be treated by endovascular methods. Conversely, angiography is probably not necessary in cases of asymptomatic unruptured mycotic aneurysms. Because endocarditis may often remain undetected by blood cultures and even echocardiography, a high index of suspicion is needed in any patient with unexplained haemorrhagic or ischaemic stroke and a cardiac murmur. Meningeal involvement is common: cerebrospinal fluid (CSF) analysis, if safe following careful clinical and radiological assessment, may suggest the diagnosis if a markedly high polymorph count is found (>100 cells/mm^3). Rheumatic fever can also cause valvular damage leading to embolism to the brain, particularly if the mitral valve is affected or atrial fibrillation develops during the illness. Sydenham's chorea is discussed in Chapter 5.

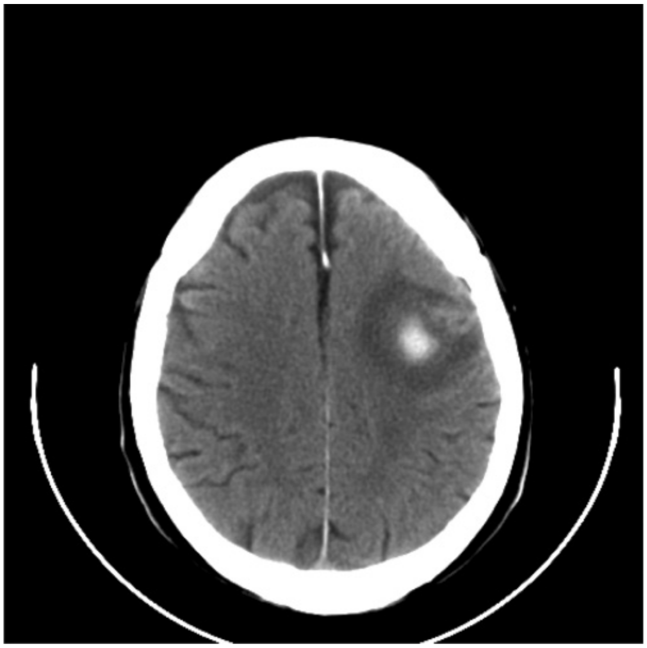

Figure 25.4 Bacterial endocarditis. Left frontal intracerebral haemorrhage in a patient with bacterial endocarditis and sudden non-fluent dysphasia. Haemorrhage may have come from a ruptured mycotic aneurysm, although no aneurysm was detected on formal angiography in this case.

Atrial myxoma

The diagnosis of atrial myxoma is challenging: myriad symptoms can occur. This often leads to long delays in diagnosis and treatment. About 30% of atrial myxomas cause cerebral emboli – accounting for about 0.4% of all strokes and stroke is the most common neurological presentation. The majority of patients (up to 90%) present with constitutional symptoms of fatigue, fever, myalgia, arthralgia and weight loss. Cardiac symptoms are often present and include breathlessness in association with congestive failure and syncope. Investigations show elevated erythrocyte sedimentation rate (ESR) and C-reactive protein, anaemia and thrombocytosis or thrombocytopenia. Chest X-ray may show left atrial or ventricular enlargement and occasionally intracardiac tumour calcification. Echocardiography is the investigation of choice, but transthoracic studies have a false negative rate of about 20%. For this reason, if clinical suspicion is high, transoesophageal echocardiography must be performed.

Stroke may result from embolic tumour fragments rather than fibrin thrombus, so anticoagulation may not be helpful and is probably best avoided, particularly as delayed cerebral aneurysm formation, often fusiform, in distal branches, can lead to cerebral haemorrhage. The treatment of atrial myxoma is optimization of cardiac function and urgent surgical removal. Follow-up with transoesophageal echocardiography is recommended as recurrence may occur, especially within the first 2 years – but occasionally more than 10 years later.

Endocrine conditions

Thyroid disease

Thyroid disorders can have a major impact on neurological function; they may affect any part of the CNS, peripheral nerves or muscle, mainly via high or low levels of circulating T4 and T3 or immune-mediated damage. It is especially important to recognize neurological manifestations of thyroid disease, as the symptoms will usually respond to appropriate treatment.

Hyperthyroidism

Hyperthyroidism is most often brought about by immune mechanisms (Graves' disease), but other causes include thyroiditis, multi-nodular goitre or, rarely, pituitary tumours. A myopathy is present to some extent in almost all patients with hyperthyroidism, although this may be asymptomatic. The onset is usually subacute, with proximal limb muscles typically affected, leading to difficulties ascending stairs, rising from a chair and raising the arms. Bulbar involvement is less common, although this may be a prominent feature in the rare acute form of thyrotoxic myopathy. Pain is common. Clinical findings are of proximal wasting especially involving shoulder and pelvic girdle muscles including quadriceps with hyper-reflexia but usually normal tone. The investigation findings usually include a normal creatine kinase (CK), in contrast to the raised CK of hypothyroid myopathy; electromyographic (EMG) abnormalities are seen, such as polyphasic motor potentials and sometimes a decrement in compound muscle action potential (CMAP) on repetitive stimulation. Rarely, hyperthyroidism can cause a form of hypokalaemic periodic paralysis, a condition seen particularly in South-East Asia.

Thyroid disease is strongly associated with myasthenia gravis, probably because susceptible individuals are genetically predisposed to autoimmune disorders. About 20% of patients with myasthenia have a thyroid disorder, more commonly hyperthyroidism than hypothyroidism.

Hyperthyroidism can also cause a dramatic upper motor neurone syndrome, particularly affecting the legs, with spasticity, weakness, clonus and extensor plantars. This can cause diagnostic confusion by mimicking spinal cord compression; lower motor neurone features may also be present causing an amyotrophic lateral sclerosis-like presentation.

Tremor is a near-invariable feature of hyperthyroidism, often most apparent in the outstretched arms. Myoclonus, chorea and even parkinsonism have also been described, albeit rarely.

Peripheral neuropathy is an uncommon but described feature of hyperthyroidism. A flaccid paraparesis with areflexia may rarely occur (Basedow's paraplegia).

Thyroid eye disease is a common feature of Graves' disease, occurring in up to 70% of patients depending on criteria used. The features of Graves' ophthalmopathy are lid retraction, inflammation of orbital soft tissues, causing redness and swelling of the lids and conjunctivae, proptosis, extraocular muscle involvement causing ophthalmoplegia, corneal damage and, rarely, optic nerve compression. MR or CT imaging are helpful in showing enlarged extraocular muscles, particularly the medial and inferior recti (Figure 25.5). Although usually both eyes are affected, some patients have markedly asymmetric involvement. Treatment includes steroids, botulinum toxin, radiotherapy or surgery.

Hyperthyroid encephalopathy is now rare, but may occur either in untreated patients, after radio-iodine treatment or during intercurrent illness or following surgical procedures. Florid signs of thyrotoxicosis, confusion, agitation, fever, seizures

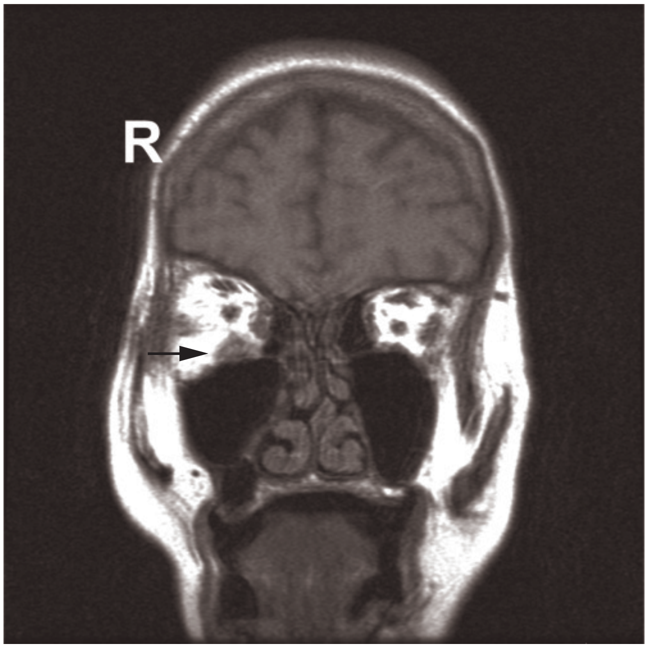

Figure 25.5 Graves' disease with progressive diplopia and restriction of right eye movements. Magnetic resonance imaging (MRI) shows enlarged inferior and medial recti on the right.

and upper motor neurone signs may all be present. Mortality from this disorder remains high.

Hypothyroidism

Hypothyroidism, resulting from immune-mediated mechanisms or following surgical or radiotherapy thyroid ablation, is an important treatable cause of neurological dysfunction affecting many parts of the nervous system.

An encephalopathy characterized by slowness, lethargy and impaired attention is commonly seen in hypothyroidism. In its most severe form, myxoedema coma, there is a substantial mortality if not recognized early and treated. Clinical features of myxoedema coma include hypothermia, depressed conscious level and usually a precipitating event such as sepsis or trauma. Early recognition and treatment with thyroid replacement (T4 and T3), antibiotics and steroids are often life-saving.

Hypothyroidism should be carefully excluded in all patients presenting with any dementing illness, because it is so readily amenable to treatment. Subtle neuropsychological features can also occur, e.g. psychosis with paranoia and hallucinations (myxoedema madness).

Cerebellar ataxia is well described and does occur, if rarely, in hypothyroidism, involving gait and the limbs, but with normal eye movements. Muscular weakness is common in hypothyroidism and sometimes an early clinical feature; it occurs in some 80% of cases if carefully sought. Weakness (usually fairly mild) is accompanied by depressed or slow-relaxing reflexes (pseudomyotonia), and typically involves the pelvic and shoulder girdles. Percussion of the muscle may cause a slow rippling effect termed myo-edema. Pain during or following muscle activity is typical of hypothyroid myopathy, and all patients presenting with unexplained muscle pains, especially related to exertion, should be screened for hypothyroidism; early treatment prevents development of more severe symptoms. The CK level is usually raised, sometimes markedly so (>10 times normal). Treatment with thyroxine improves matters, usually promptly but in advanced cases it is sometimes over a year before the situation recovers fully.

Hypothyroidism also causes peripheral nerve problems. An entrapment neuropathy, most frequently carpal tunnel syndrome, is seen in some 10% of hypothyroid patients. A useful working rule is to check the thyroid function in all suspected carpal tunnel cases. Treatment is restoration of the euthyroid state rather than surgical decompression. A polyneuropathy develops in up to two-thirds of hypothyroid patients, usually mild and mainly sensory.

Neurological aspects of Hashimoto's thyroiditis

The possible relationship between thyroid antibodies and encephalopathy has been debated since the 1960s. The term Hashimoto encephalopathy describes a subacute, sometimes relapsing encephalopathy, responding well to corticosteroids and associated with a high titre of antithyroid antibodies. The encephalopathy in such cases is not explained by thyroid status, which may be normal. The term Hashimoto's encephalopathy has been criticized as it implies that the antibodies are pathogenic in the development of encephalopathy, a link for which there is little convincing evidence. It has been suggested that the thyroid antibodies may be epiphenomena, and indeed they may be seen in encephalopathies known to have an alternative cause. It is therefore important to try to establish a definitive diagnosis for an encephalopathy associated with antithyroid antibodies. For example, the recently described syndrome of encephalopathy with antibodies to voltage gated potassium channels may also need to be considered. Sometimes, invasive tests including cerebral biopsy are needed.

Diabetes mellitus

Diabetes mellitus can cause many effects on the nervous system. Rare congenital causes of diabetes that may be encountered by neurologists include mitochondrial cytopathies, particularly patients with sensorineural deafness but also those with MELAS or Kearns–Sayre syndrome (Chapter 9), Friedreich's ataxia and Wolfram's syndrome (Type 1 diabetes, diabetes insipidus, optic atrophy and deafness [DIDMOAD]). The other main neurological conditions where diabetes can be highly important are acute metabolic disturbances (related to hyperglycaemia or hypoglycaemia) and the diabetic neuropathies.

Acute metabolic disturbances

Diabetic ketoacidosis occurs because of insufficient insulin levels in patients with Type 1 diabetes, usually because of undertreatment with insulin or its omission, with or without an intercurrent illness such as sepsis. Drowsiness occurs but not usually coma. Very rarely, cerebral oedema can develop during treatment because of over-rapid correction of hyperosmolality, especially in children. This can cause death from raised intracranial pressure. Hyper-osmolar non-ketotic coma (HONK) occurs mainly in patients with Type 2 diabetes and may lead to very high blood glucose with high sodium levels and therefore high osmolality. Reduced conscious level or seizures may occur. Conversely, low blood glucose can result from excessive doses of oral hypoglycaemics or insulin. With a low blood sugar, there is often a warning prodrome, allowing the patient to react and correct the problem, but in some patients with Type 1 diabetes the warning is absent, placing them at much greater risk of prolonged hypoglycaemia. Early warning symptoms include sweating, trembling, tingling hands and palpitations. Neurological features can include confusion, dysarthria, altered behaviour and agitation, seizures and, albeit rarely, focal neurological features (e.g. hemiparesis or hemiplegia) that can mimic a TIA or stroke.

Diabetic neuropathies

The neuropathies caused by diabetes are covered in detail in Chapter 9. The most common is a distal sensorimotor neuropathy, affecting over 50% of patients with long-standing disease. Rarer variants include diabetic autonomic neuropathy, acute painful neuropathy, cranial neuropathy (especially oculomotor), thoraco-abdominal neuropathy and painful proximal neuropathy (diabetic amyotrophy).

Pituitary disorders

Pituitary tumours are discussed in Chapter 20. Pituitary neoplasms either produce an excess of hormone secretion (in about two-thirds) or non-functioning – sometimes causing deficiency by mass effects (in about one-third). Tumours secreting prolactin (prolactinomas) cause secondary amenorrhoea, galactorrhoea, infertility and impotence. Other clinical syndromes include acromegaly (resulting from growth hormone secretion) and Cushing's disease (resulting from adenocorticotrophic hormone [ACTH] secretion). Pituitary tumours can present with visual disturbances, including visual failure, headaches, and endocrine features, or simply with an unexplained high serum prolactin. Non-secreting tumours may cause hypopituitarism, with secondary amenorrhoea, infertility or impotence, loss of secondary sexual characteristics or hypothyroidism.

Diabetes insipidus results from dysfunction of the posterior pituitary. Reduced secretion of arginine vasopressin and antidiuretic hormone cause symptoms of thirst, polyuria and polydipsia. The common caues are trauma, tumours, sarcoidosis and other granulomatous conditions, and infections. Sarcoidosis is considered below.

Pituitary apoplexy (Sheehan's syndrome, Chapter 20) is a dramatic clinical syndrome of severe headache, nausea, vomiting and often hypotensive collapse with sudden bilateral visual loss. The usual cause is haemorrhage into a pituitary macroadenoma.

Inappropriate antidiuretic hormone secretion (SIADH) and cerebral salt wasting

These conditions are discussed in Chapter 19.

Parathyroid glands

In cases of hypoparathyroidism (or pseudohypoparathyroidism, a rare familial form with skeletal and developmental anomalies) the reduction in serum ionic calcium may cause sensory disturbances, tetany, chorea or seizures (Table 25.2); basal ganglia or

Table 25.2 Causes and features of common electrolyte disturbances.

Electolyte disturbance	Causes	Clinical features
Hyponatraemia	SIADH Cerebral salt wasting Diuretic use Addison's disease Drugs (e.g. carbamazepine) Liver disease Cardiac failure	Coma Confusion Convulsions (<115 mmol/L)
Hypernatraemia	Diabetes insipidus HONK Diarrhoea Dehydration	Reduced conscious level Seizures Tremor Movement disorders
Hypokalaemia	Diarrhoea Vomiting	Generalized muscle weakness
Hyperkalaemia		Generalized muscle weakness ECG changes Cardiac arrest
Hypocalcaemia	Hypoparathyroidism	Paraesthesias Tetany Seizures, chorea Encephalopathy Papilloedema & ↑ ICP Coma
Hypercalcaemia	Hyperparathyroidism Osteolytic bone malignancy Immobility Sarcoidosis Vitamin D intoxication	Anorexia, abdominal pain Nausea Fatigue Reduced conscious level Constipation Myoclonus, rigidity Elevated CSF protein
Hypomagnesaemia	Rarely isolated – usually part of complex electrolyte derangement	
Hypermagnesaemia	Rare Iatrogenic (e.g. treatment of eclamptic seizures)	

CSF, cerebrospinal fluid; ECG, electrocardiography; HONK, hyper-osmolar non-ketotic coma; ICP, intracerebral pressure; SIADH, syndrome of inappropriate antidiuretic hormone.

cerebellar calcification may also occur. Hyperparathyroidism resulting from parathyroid adenoma or hyperplasia causes muscle weakness, fatiguability and amyotrophy with preserved reflexes, and has been reported on occasion to resemble motor neurone disease.

Adrenal glands

Cushing's disease

Cushing's disease results from pituitary hypersecretion of ACTH and thus high plasma cortisol, most often from a pituitary microadenoma. Note the difference between Cushing's disease and Cushing's syndrome, the latter being a result of treatment with exogenous steroids or primary hyperadrenalism. Clinically, the disease and the syndrome are indistinguishable, both being characterized by centripetal obesity, hypertension, hirsutism, abdominal striae, acne, menstrual irregularity, immunosuppression, myopathy and psychosis. Cushing's disease is usually caused by a microadenoma that typically does not cause visual symptoms.

Addison's disease

Addison's is caused by adrenal insufficiency. In the past, tuberculosis was a common cause, but now an autoimmune mechanism is the cause in most cases. A rare cause is adrenoleucodystrophy, in which brain and spinal cord involvement cause other neurological features of varying severity (Chapter 10). The important features of Addison's disease are a tendency to faint – or episodes of unexplained coma or episodes of stupor, weight loss, apathy and vomiting with pigmentation of the skin and mucous membranes. The condition can be life-threatening, especially during intercurrent illnesses. The laboratory findings are of low serum sodium, high potassium and low serum cortisol.

Phaeochromocytoma

Phaeochromocytoma is a neuroendocrine catecholamine secreting tumour of the adrenal medulla and is an important cause of hypertension, especially in younger people. Tumours are often multiple and sometimes extramedullary (paragangliomas). Other clinical features include panic, anxiety, palpitations, headaches and weight loss. Neurological features are rare, but can include those of accelerated hypertension, including intracranial haemorrhage and hypertensive encephalopathy.

Electrolyte disturbances

Electrolyte abnormalities are extremely common in acute and out-patient practice; their effects range from being asymptomatic to causing profound disturbance of function in the central and peripheral nervous system. As a general principle, the clinical severity of any electrolyte disturbance is greatest when the abnormality has developed rapidly. Treatment is aimed at not only correcting the electrolyte disturbance itself, but also identifying and treating the cause. The central nervous system effects of electrolyte imbalance, often including altered consciousness and seizures, are related to fluid shifts and brain volume changes. Serum hyperosmolality causes brain shrinkage, while hypo-osmolality causes brain swelling. Other mechanisms include disordered transmembrane potentials and neurotransmission. The clinical features of abnormalities in serum sodium, potassium, calcium and magnesium are summarized in Table 25.2 and are briefly discussed here.

Sodium

Neurological effects of sodium disturbances are covered in detail in Chapter 19. SIADH may be a consequence of a number of intracerebral pathologies including meningo-encephalitis or subarachnoid haemorrhage. Because the diagnosis can be made only when the serum is dilute and the urine inappropriately concentrated, osmolality measurements are critical in the evaluation of hyponatraemia. The rapid correction of serum sodium may cause the distinct syndrome of central pontine myelinolysis (Chapter 19) – the fully developed syndrome of a quadriparesis with brainstem signs carries a high mortality. This syndrome is more common in high risk groups such as alcoholics.

Hyponatraemia may be a clue to a recently described autoimmune disorder of an encephalopathy resembling limbic encephalitis associated with antibodies against voltage gated potassium channels. This syndrome is associated with SIADH and consequent hyponatraemia.

Potassium

Hyperkalaemia or hypokalaemia are features of periodic paralysis (Chapter 9). Indeed, the main neurological effect of low (or sometimes high) serum potassium is generalized muscle weakness. Serum potassium must always be checked in anyone with weakness.

Calcium and magnesium

Disturbances of calcium metabolism sometimes present to a neurologist and should be sought in cases of tetany, seizures or occasionally chorea. Hypocalcaemia may lead to calcification in the basal ganglia, usually found coincidentally on imaging. Hypomagnesaemia may be a feature of eclamptic seizures and should be treated in this context.

Haematological disorders

This section considers anaemias, haematological proliferative disorders, bleeding diatheses and coagulation disorders. Haematological disorders and stroke are discussed in the chapter on cerebrovascular diseases (Chapter 4) and are briefly mentioned here.

Anaemias

Anaemias generally cause rather non-specific symptoms including fatigue, dizziness, impaired concentration, faintness and syncope, irritability and headache; a full blood count should always be performed to exclude anaemia as a cause of these symptoms, and those of chronic daily headache. Occasionally, severe anaemia (less than 8 g/dL) can cause focal neurological deficits, and TIAs in the presence of a significant atherosclerotic stenosis in an extracranial or intracranial vessel. Iron deficiency anaemia has been reported to be associated with idiopathic intracranial hypertension, with response to treatment of the anaemia. Iron deficiency is also associated with the restless leg syndrome (Chapter 19), sometimes with normal haemoglobin but a reduced serum ferritin. Retinal haemorrhages are sometimes seen with very severe anaemias, especially with B_{12} deficiency.

Vitamin B_{12} deficiency, one cause of megaloblastic anaemia, is an important and potentially treatable cause of neurological symptoms and signs and discussed in detail elsewhere (Chapter 18). B_{12} deficiency can cause many different neurological syndromes – peripheral neuropathy with or without myelopathy (together known as subacute combined degeneration of the cord), encephalopathy, dementia, optic neuropathy and ophthalmoplegia. Folic acid can mask the anaemia without preventing the neurological sequelae. Before the discovery of vitamin B_{12}, subacute combined degeneration of the cord was fatal. Treatment is with long-term hydrocobalamin injections. Measurement of serum homocysteine should be carried out if the serum vitamin B_{12} level is non-diagnostic and there is clinical suspicion of deficiency. Low serum copper is also a rare cause of a syndrome resembling subacute combined degeneration of the cord.

Sickle cell disease causes neurological symptoms from intravascular sickling of erythrocytes via a number of mechanisms including large vessel arteriopathy, small perforating vessel occlusion, haemolysis, abnormal vasomotor tone and promotion of a hypercoaguable state. The incidence of stroke in sickle cell disease is much higher than in the general population. Sickling is exacerbated by low oxygen saturation and/or intercurrent illness. Small vessels may be occluded to cause subcortical infarction (usually not acutely symptomatic) while large vessels (especially the supraclinoid intracranial internal carotid and proximal middle cerebral arteries) can develop intimal proliferation causing stenosis and thrombo-embolism (often symptomatic). In patients with overt large artery stroke there is commonly distal collateral formation (secondary Moyamoya changes). Subacute or chronic symptoms include headaches, which may be migrainous, and cognitive impairment caused by the accumulation of ischaemic damage. Haemorrhagic complications of sickle cell disease can occur in adults, especially subarachnoid haemorrhage. Neurological symptoms have been found to occur in some 25% of patients with sickle cell disease, while up to one-third have imaging evidence of cerebrovascular disease. Treatments available to prevent the neurological consequences of sickle cell disease include partial-exchange transfusion, hydroxyurea and bone marrow transplantation.

Thalassaemia is a rare cause of neurological symptoms. Haematopoeisis outside the marrow may occur in lymphoid tissue, spleen, liver and bone. Myelopathy has been described and attributed to haematopoietic tissue in the epidural space. Corticosteroids, radiotherapy, blood transfusions and surgical decompression have been used in this situation.

Proliferative conditions

Leukaemias

Leukaemia can cause neurological symptoms by direct infiltration of nervous tissue or indirectly by haemorrhage related to low platelets, from infection resulting from impaired immunity, electrolyte disturbances or hyperviscosity.

Leukaemic cells enter the nervous system by haematogenous seeding, lymphatic spread or direct invasion by spread along the meninges. Meningeal leukaemia is most commonly associated with acute lymphocytic leukaemia (ALL) and presents as a subacute meningitic syndrome with headache, drowsiness, neck stiffness, irritability and cranial neuropathy, especially affecting the optic, oculomotor, abducens, facial and vestibulocochlear nerves. Papilloedema is commonly seen. Raised CSF protein may impair CSF resorption leading to hydrocephalus. The CSF contains leukaemic cells and usually a high protein, although repeated lumbar puncture may be needed to establish a diagnosis.

Solid leukaemic deposits may occur in any part of the CNS, although the brain is more commonly affected than the spine. Peripheral nerve involvement is unusual.

Plasma cell dyscrasias

Plasma cell dyscrasias are conditions resulting from the proliferation of a single clone of immunoglobulin-secreting plasma cells (activated B cells). The antibodies secreted by the proliferating clone are classified into IgM, IgG and IgA types according to their heavy-chain class, from which are derived various terms including monoclonal gammopathy, M-protein and other paraproteins. All patients with neuropathy should be tested for a paraprotein.

The plasma cell dyscrasias include myeloma (multiple myeloma and osteosclerotic myeloma), Waldenstrom's macroglobulinaemia, monoclonal gammopathy of undetermined significance (MGUS), plasmacytoma and plasma cell leukaemia.

Multiple myeloma affects bones causing pain, fractures and sometimes compression of neural tissue. Myeloma involving the vertebrae is a common cause of spinal cord compression; the development of the paraparesis is usually preceded by back pain for several months. The cauda equina and nerve roots may be compromised by direct infiltration. Meningeal involvement can also cause cranial neuropathies; occasionally such meningeal infiltration may be the only manifestation of myeloma. A peripheral neuropathy may result from either a paraneoplastic mechanism, amyloid deposition compromising nerve blood supply or direct infiltration of nerves.

Waldenstrom's macroglobulinaemia is a hyperviscosity syndrome associated with an IgM gammopathy and involves the nervous system in about 25% of cases. A progressive sensorimotor neuropathy results from IgM antibody binding and/or lymphocytic infiltration. The hyperviscosity may cause focal neurological deficits including strokes and an encephalopathy with headache. Patients also have a bleeding tendency and may develop bruising, purpura and subarachnoid haemorrhage.

MGUS is a benign condition, but some patients ultimately develop a malignant plasma cell dyscrasia; the paraprotein level should be monitored 6–12 monthly. A chronic inflammatory demyelinating peripheral neuropathy (CIDP) may be associated.

Lymphomas

Lymphoma, both of Hodgkin's and non-Hodgkin's type, can affect the nervous system. Usually patients will have evidence of lymphoma elsewhere and the disease spreads directly to CNS tissue. Spinal cord disease (solid tumours) and meningeal infiltration are common manifestations of lymphoma. Extradural deposits may compromise the blood supply of the cord to cause an ischaemic myelopathy or may exert a direct compressive effect. The cauda equina and lumbosacral roots may be infiltrated causing painful radicular syndromes. Meningeal lymphoma can have a chronic clinical course, sometimes with spontaneous temporary remission. The hemispheres, cerebellum or brainstem may be infiltrated to cause focal signs and elevated intracranial pressure. A number of lymphoma-associated paraneoplastic syndromes have been described, including peripheral neuropathy, necrotizing myelopathy, leucoencephalopathy and polymyositis (Chapter 20).

Primary CNS lymphomas are rare, constituting only 1% of primary brain neoplasms. They are typically of B-cell origin and affect principally individuals with impaired immunity, including transplant recipients, patients with HIV and inherited immunodeficiency disorders. The tumours are usually ill-defined lesions in the cerebral hemispheres, ventricles, corpus callosum, basal ganglia and cerebellum. Lymphoma may respond dramatically but temporarily to corticosteroids in the early stages, which can cause diagnostic confusion. Lymphoma may also present with focal symptoms or encephalopathy and/or seizures and nodular enhancing lesions in the ventricular wall. The differential diagnosis of cerebral lymphoma is wide and includes metastatic carcinoma, glioma, tuberculosis, toxoplasmosis, neuro-cysticercosis and sarcoidosis. A tissue diagnosis is usually essential. For a more detailed discussion of primary CNS lymphoma see Chapter 20.

Polycythaemia

Polycythaemia is an increased red cell mass causing a raised haematocrit. It may be primary (polycythaemia vera) or secondary to another condition (e.g. chronic hypoxia). The symptoms of polycythaemia may be generalized and rather ill-defined (including poor concentration, feelings of cephalic fullness, tinnitus, paraesthesias) or acute focal vascular syndromes, either permanent or transient. These may be due to arterial or venous events. Chorea is associated with polycythemia vera (recently found to be related to a mutation in the erythropoietin receptor gene, *JAK2*) and may respond to treatment of the polycythaemia. Polycythaemia vera can transform into other haematological malignancies (e.g. leukaemias, myelofibrosis). The mainstay of treatment of polycythaemia is repeated venesection.

Thrombocythaemia

Thrombocythaemia (platelet count >800,000/mm^3) is associated with an increased risk of thrombosis and haemorrhage within the CNS. It may be associated with leukaemia or myelodysplasia. Thrombosis can occur in arteries, veins or venous sinuses and is related to hyperviscosity. Haemorrhage can also occur (subdural, extradural, intracerebral, subarachnoid); the mechanism presumably involves abnormal platelet function. Treatment with hydroxyurea is usually recommended to prevent neurological symptoms.

Bleeding disorders

Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP) is a rare disorder of early adulthood characterized by recurrent and widespread occlusion of small vessels. The pathophysiology involves micro-angiopathic haemolysis and formation of platelet micro-thrombi throughout the body including the nervous system. TTP may be familial or acquired but in both cases endothelial cells secrete abnormally large von Willebrand factor multimers that are not degraded because of the lack of the cleavage enzyme ADAMTS-13. This allows the formation of platelet thrombi in small vessels. The clinical hallmarks are fevers, hepatic and renal disease and a low platelet count. Fragmented red cells on the blood film, elevated lactate dehydrogenase, bilirubin and reticulocyte count also point towards the diagnosis. Fluctuating neurological symptoms of altered conscious level, seizures, headache or encephalopathy may be the presenting feature in half of the patients and may be preceded by a provoking factor such as an intercurrent illness. The majority of patients will at some stage of the illness develop neurological symptoms. Low platelets lead to haemorrhage including intracerebral haemorrhage. Ischaemic stroke from large or small vessel occlusion may occur. The mainstay of treatment is plasma exchange. Antiplatelet agents or anticoagulants may also be used although evidence for efficacy is lacking. Other immunomodulatory treatments have been used including ciclosporin. Rituximab is the subject of ongoing investigation.

Haemophilia, disseminated intravascular coagulation and von Willebrand's disease are also rare causes of intracerebral haemorrhage.

Coagulation disorders

The antiphospholipid antibody syndrome (Chapter 4), although usually characterized by venous thromboses, is also an important rare cause of arterial cerebrovascular events, sometimes in association with skin rashes, migraine and recurrent miscarriage. Thrombophilias including protein C and S deficiency, antithrombin III deficiency, factor V Leiden and the *MTHFR* mutation are associated with cerebral venous thrombosis, but not strongly with arterial events. These disorders are also discussed in more detail in Chapter 4.

Gastrointestinal disorders

Hepatic encephalopathy

In severe hepatic failure, toxins are not removed from portal blood and thus enter the systemic circulation. The toxins responsible for hepatic encephalopathy include ammonia, aromatic amino acids, mercaptans, short-chain fatty acids and endogenous benzodiazepines. The speed of onset of encephalopathy parallels that of the underlying hepatic failure; this may vary from hours to very slow progression over months. Delirium typically fluctuates during the day and may be accompanied by euphoria and neurological signs including a flapping postural tremor of the hands (asterixis) and constructional apraxia. Hepatic foetor is the sickly sweet odour on the breath found in many cases. Untreated, delirium progresses to stupor and coma. Treatment is mainly aimed at reducing the nitrogen burden in the bowel – a low protein diet, regular large doses of lactulose and sometimes neomycin. Hepatic transplantation may be required.

Malabsorption and coeliac disease

Malabsorption is either the result of gluten sensitivity or many other processes affecting the small bowel, including surgical resection.

Vitamin B_1 deficiency

Vitamin B_1 (thiamine) deficiency causes Wernicke's encephalopathy, Korsakoff's syndrome and beri-beri (see Chapter 18). Wernicke's encephalopathy is a subacute illness causing delirium, nystagmus – with or without ophthalmoplegia – and ataxia, typically of gait more than limbs. The syndrome is underdiagnosed and potentially treatable. Korsakoff's can follow Wernicke's encephalopathy and is characterized by a more restricted syndrome of anterograde and retrograde amnesia without delirium. Although classically a result of chronic alcoholism, Wernicke's encephalopathy and Korsakoff's syndrome are well known to result from other causes, such as intractable vomiting (e.g. anorexia nervosa, hyperemesis gravidarum). One of the three patients originally reported by Wernicke suffered from severe vomiting from pyloric stenosis induced by sulphuric acid poisoning.

The extent of recovery is influenced by the time to diagnosis and treatment with thiamine. Some of the eye signs and ataxia often resolve but a residual amnestic syndrome is common. In any patient with cognitive disturbance or delirium in the context of heavy alcohol use, prompt treatment with high dose intravenous B vitamins is recommended – it rarely causes harm.

Pellagra (niacin deficiency)

Endemic niacin deficiency is rarely seen in developed countries, but is characterized by dementia, dermatitis and diarrhoea (the three D's). The most common cause of pellagra now is chronic alcoholism, which usually presents with acute and isolated delirium. There can also be generalized rigidity (sometimes cogwheeling), dysarthria and myoclonus.

Vitamin D deficiency

Proximal muscle weakness can develop as a result of vitamin D malabsorption. The symptoms usually start in the legs, affecting hip movements but with preservation of distal power, reflexes and sensation. EMG may show myopathic features with short duration polyphasic potentials. The degree of muscle weakness is not correlated with plasma calcium concentration and the underlying mechanism is unclear. Vitamin D treatment is generally helpful.

Vitamin E deficiency

Vitamin E deficiency results from cholestatic liver disease, fat malabsorption, abetalipoproteinaemia or as a familial absorption disorder. The clinical features include neuropathy, ataxia, ophthalmoplegia and muscle weakness. A familial condition with poor conservation of plasma α-tocopherol in very low density lipoproteins is characterized by ataxia, cerebellar signs, dysarthria, leg areflexia, impaired proprioception, bilateral extensor plantar responses, pes cavus and scoliosis. These signs are strikingly similar to those seen in Friedreich's ataxia (Chapter 16). All patients presenting with an unexplained spinocerebellar syndrome or tremor should have vitamin E concentrations measured, as the symptoms may respond to treatment.

Coeliac disease

Many neurological syndromes affecting the central and peripheral nervous systems have been reported in association with coeliac disease, including epilepsy, myoclonus, ataxia, multifocal leucoencephalopathy, dementia and peripheral neuropathies, both axonal and demyelinating. It is speculated that immunological mechanisms or trace vitamin deficiency underly these associations. Substantial neurological features can occur in the absence of overt coeliac disease. Coeliac disease should certainly be considered in cryptogenic ataxias and neuropathies (Chapter 16).

Infective and para-infective disorders

These are discussed in Chapters 8 and 9.

Renal disease

Renal diseases may be relevant to neurologists in two main ways. First, certain diseases affect both the kidneys and the nervous system – these include the vasculitides and connective tissue diseases as well as serious conditions including genetic disorders (Anderson–Fabry disease, Wilson's disease, von Hippel–Lindau disease) infections and plasma cell dyscrasias. Secondly, renal failure, dialysis and renal transplantation can all affect neurological function in a variety of ways.

Conditions affecting both renal and neurological function

These conditions are mainly covered in other sections; the key features of some selected conditions are briefly summarized in

Table 25.3 Conditions affecting renal and neurological function.

Condition	Renal effects	Neurological effects
Vasculitis		
PAN	Proteinuria, granular casts, hypertension	Peripheral neuropathy, encephalopathy, stroke (infarction and SAH)
Churg–Strauss syndrome	Rarely involved	Mononeuritis multiplex encephalopathy, SAH
Wegener's granulomatosis	Proteinuria, haematuria, red cell casts, renal failure	Cranial neuropathies, mononeuropathies, polyneuropathy, ischaemic stroke
Connective tissue disorders		
Rheumatoid disease	Glomerulonephritis (rare)	Polyneuropathy, mononeuropathies, cervical cord damage due to bony disease
SLE	Haematuria, proteinuria, nephritic syndrome, renal failure	Neuropsychiatric symptoms, encephalopathy, seizures, ischaemic stroke, chorea
Sjögren's syndrome	Tubular disorders	Dorsal roots ganglionopathy, neuropathy, cranial neuropathy (especially V), encephalopathy, MS-like symptoms
Myeloproliferative disorders		
Multiple myeloma	Proteinuria, Bence-Jones protein, nephrotic syndrome	Nerve root/cord compromise
MGUS	Rarely abnormal	Demyelinating sensory > motor peripheral neuropathy
Waldenstrom's macroglobulinaemia	Proteinuria, nephrotic syndrome	Sensorimotor neuropathy, encephalopathy, SAH, stroke, myelopathy
POEMS	Rarely, M protein in urine	Demyelinating neuropathy (sensory > motor) resembling CIDP (50%)

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; MGUS, monoclonal gammopathy of undetermined significance; MS, multiple sclerosis; PAN, polyarteritis nodosa; POEMS, Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, Skin changes.

Table 25.3. A neurologist should remember that renal disease in its early stages causes few or no symptoms and that renal function must therefore be screened when there is even a small degree of clinical suspicion. Vigilance is important; the consequences of progressive renal disease are severe and potentially avoidable. Routine biochemistry (urea and creatinine) are but crude measures of renal impairment. If renal disease is questioned (e.g. a patient with a mononeuritis multiplex), urine microscopy for casts and detailed urinalysis, close monitoring of blood pressure and renal ultrasound should all be performed without delay.

Neurological consequences of renal disease and its treatment

Uraemic encephalopathy

Neurological manifestations are usually associated with the rapid development of uraemia in acute renal failure. The onset is with subtle clouding of consciousness that may progress rapidly to apathy, irritability, confusion and disorientation. A coarse irregular tremor with asterixis can develop. Severe metabolic encephalopathy associated with uraemia is also associated with a progressive stimulus-sensitive multi-focal myoclonus and eventually the development of generalized tonic–clonic or focal motor seizures. Frank psychosis and agitation with hallucinations may supervene before the development of uraemic coma, Cheyne–Stokes respiration and respiratory arrest. Uraemic encephalopathy is generally reversible with recovery from acute uraemia.

Dialysis encephalopathy

Dialysis encephalopathy (dialysis dementia) is the rare but potentially fatal condition that previously complicated chronic dialysis and is still occasionally seen. Patients develop subacute progression of fluctuating symptoms in the early stages which either become fixed or progress. The condition is characterized by dysarthria, dysphasia and progressive metabolic encephalopathy with myoclonus and asterixis, culminating in generalized seizures and intellectual decline. The syndrome is caused by the aluminium content in gels and dialysate solution. Treatment with purified dialysate has led to the disappearance (almost) of this condition. Chronic haemodialysis can also lead to Wernicke's encephalopathy, sensorimotor axonal polyneuropathy and occasionally subdural haematoma.

Dialysis disequilibrium syndrome

This is related to changing osmotic gradients between plasma and brain during rapid dialysis. It can present with non-specific symptoms of nausea, visual blurring and headache prior to development of worsening mental confusion, clouding of consciousness, seizures and tremor. The symptoms are usually mild and can be alleviated with slow flow rates during dialysis and the addition of osmotically active solutes to the dialysate.

Neuropathy associated with renal disease

Uraemic neuropathy is a distal axonal degeneration with secondary myelin loss. This occurs in the majority of patients with chronic renal failure; the severity is related to the extent and duration of renal failure. Onset is often with periodic limb movements or restless legs and established neuropathy is characterized by a distal paraesthetic sensory disturbance. The neuropathy is reversible with treatment of the renal failure.

Neurological aspects of organ transplantation

Organ transplantation is now widely undertaken. Kidney, liver, heart, lung, pancreas and bone marrow are successfully transplanted with relatively low morbidity and mortality. The neurological complications of these procedures are related to the effects of the underlying organ failure, immunosuppression leading to secondary infection, allograft rejection, effects of drug treatment or consequences of the surgical procedure. The neurological complications vary with time following surgery.

CNS infections

CNS infections develop in less than 10% of transplant recipients and in immunosuppressed patients; these can be severe and carry a high mortality. Infections in the immunosuppressed patient are discussed in Chapter 8 but a number of issues relate specifically to post-transplant patients. The risk of infection depends on the degree of immunosuppression, the intensity of exposure to potential pathogens and the time since transplantation. It is rare for opportunistic infection to develop within 1 month of surgery and commencing immunosuppression. During this period, infection is unrelated to the degree of immunosuppression, and is usually caused by the regular nosocomial organisms such as Gram-negative bacteria, staphylococci and *Candida*. Patients are predisposed to these infections, as is anyone critically ill, by contamination of vascular access or drainage catheters, prolonged intubation, stents or other foreign bodies and fluid collections. Rarely, active toxoplasmosis and viral infections may be passed with the graft.

More than 1 month after transplantation, as effective immunosuppression develops, the patient is at increased risk of infection with viruses (cytomegalovirus [CMV], Epstein–Barr virus [EBV], herpes simplex virus [HSV], varicella-zoster virus [VZV] and human herpesvirus [HHV]) and fungi (*Aspergillus* and *Candida*). Most patients with successful transplants are maintained on low-dose immunosuppression and are not at particularly high risk of late opportunistic infection.

More than 6 months after transplantation, infection may occur if the degree of immunosuppression has been increased because of recurrent or chronic allograft rejection. These patients are at particular risk of opportunistic infections listed above but also with other viruses (e.g. JC virus), fungi (*Aspergillus, Cryptococcus, Nocardia, Histoplasmosis, Mucor*), protozoa (toxoplasmosis) or bacteria (*Listeria monocytogenes, Pneumocystis carinii,* mycobacteria).

Viral infection

The pattern of opportunistic viral infection following transplantation is highly variable. The most frequent pathogens are EBV, VZV, adenoviruses, and herpes viruses HSV1 & HSV2; HHV6 is less common. CMV and EMV may cause severe encephalitis which can be difficult to diagnose. Reactivation of VZV may lead to cutaneous dissemination (chickenpox) and/or a generalized meningo-encephalitis, transverse myelitis and cranial neuropathy. Progressive multi-focal leucoencephalopathy (Chapter 8) is associated with JC virus infection and must be distinguished in the post-transplant encephalopathic patient from central pontine myelinolysis and posterior reversible leucoencephalopathy related to treatment.

Bacterial infection

Bacterial infection in the transplant patient is less common than viral but can be caused by *Listeria monocytogenes* which causes meningo-encephalitis, often with a brainstem emphasis, multiple abscess formation or myelitis. Mycobacteria can cause pulmonary tuberculosis, TB meningitis or atypical TB CNS infection. Haemophilus or staphylococcal pneumonia and/or meningitis also occur in post-transplant patients. *Nocardia* infection is associated with cerebral abscess formation and often with pleural disease.

Fungal infection

Fungal meningitis (Chapter 8) is most commonly caused by *Aspergillus* in the first 6 months while typically *Cryptococcus* develops later than 6 months.

Aspergillus species occur commonly in the environment. Primary infection is usually airborne and established in the lungs. Spread to the CNS occurs in some 50% of cases. This carries an extremely poor prognosis because of the development of severe meningitis, focal aspergilloma brain abscesses and invasion of the cerebral vessels leading to intracerebral haematomas. The spinal cord may also be occasionally affected. Disseminated cryptococcosis involves the CSF and can cause severe chronic relapsing meningitis with raised intracranial pressure. There is a high mortality in transplant recipients. *Candida* meningitis is a rare post-transplant infection with chronic relapsing meningitis and/or brain abscess formation; this usually responds well to aggressive antifungal treatment. *Mucor* is an occasional CNS infection.

Parasitic infection

Toxoplasma gondii is the most frequent protozoa to infect transplant recipients. The pattern of single or multiple enhancing cerebral abscesses is similar to that described in other immunosuppressive situations in Chapter 8. There may also be an acute encephalitis, occasionally with myocardial involvement. The CSF shows marked mononuclear pleocytosis with elevated protein, sometimes with depressed glucose. MRI shows characteristic ring enhancing abscesses, often in the basal ganglia.

Neurological sequelae of transplantation

Seizures

Seizures are relatively common in transplant recipients and have a number of causes. They commonly occur as a manifestation of drug toxicity (especially with ciclosporin and OKT3). Seizures may also be associated with drug withdrawal, metabolic derangements, hypoxic ischaemic injury, cerebrovascular disease and sepsis. The initial management is correction of the underlying disturbance but in patients with ongoing impairment of consciousness it is essential to exclude non-convulsive status. Status epilepticus is treated conventionally, with benzodiazepines and phenytoin. However, titration of these drugs may be difficult because of renal and hepatic impairment, and hypoalbuminaemia. Isolated seizures following organ transplantation rarely lead to long-term epilepsy and therefore anticonvulsant medications are seldom required when the acute episode has resolved.

Encephalopathy

Encephalopathy develops commonly following transplantation and varies from a mild confusional state to psychosis with obtundation and coma. In the acute postoperative situation it is often brought about by a surgical complication (e.g. hypoxic-ischaemic insult), the development of a metabolic encephalopathy, acute allograft rejection, isolated or multiple organ failure, sepsis, seizures or drug toxicity (particularly ciclosporin).

Stroke

Stroke following transplantation is an important cause of morbidity and mortality. It is often related to the underlying disease process and in particular accelerated cerebrovascular atherosclerosis in diabetes mellitus. Stroke may also be a consequence of cardiogenic emboli and CNS infections that cause vasculopathy or vasculitis. Cardiac transplantation carries the complications of bypass – cardio-embolic stroke, air embolism and bacterial endocarditis.

Fungal CNS infections (particularly aspergillosis and mucormycosis) are associated with invasion and occlusion of the cerebral vessels resulting in haemorrhagic infarction.

Medication including ciclosporin and sirolimus and, to a lesser extent, tacrolimus may also lead to hypocholesterolaemia.

Intracerebral haemorrhage is usually seen in the setting of haemorrhagic transformation of an ischaemic stroke, resulting from coagulopathy or following CNS infection. Subdural haematoma may occur with thrombocytopenia, particularly following bone marrow transplantation. Subarachnoid haemorrhage is particularly associated with the increased incidence of berry aneurysms that may rupture following renal transplantation for polycystic disease. Cerebral venous thrombosis can occur as a consequence of a hypercoagulable state, dehydration or CNS infection.

Medication

Complications of immunosuppressive drugs are also discussed in Chapters 20 and 18. The drugs most frequently causing neurotoxicity are ciclosporin, tacrolimus, steroids and OKT3.

Ciclosporin neurotoxicity occurs in some 25% of patients and includes tremor, headache and, less commonly, posterior reversible encephalopathy. The complications are lessened with oral administration and are usually reversible with discontinuation of the drug. Profound impairment in cognitive function has also been reported to be associated with tacrolimus and ciclosporin. OKT3 is a murine E monoclonal antibody used in the treatment of rejection and has been associated with aseptic meningitis, encephalopathy and seizures.

The combination of steroids with neuromuscular junction blocking agents may cause prolonged neuromuscular blockade or a critical illness myopathy.

CNS malignancy

There is an increased incidence of CNS malignancy in allograft recipients who are immunosuppressed. Intracerebral B-cell lymphoma affecting the brain and spinal cord and glioblastoma multiforme are the most common CNS cancers. They may be associated with previous EBV infection.

Neuro-ophthalmological problems

Cortical blindness, complex visual disturbances and hallucinations, not uncommon in all critically ill patients, may be caused by dose-related toxicity from tacrolimus or ciclosporin. This is often reversible.

Movement disorders

Both ciclosporin and tacrolimus are associated with a high incidence of tremor. Occasionally, parkinsonism has been described in bone marrow transplant recipients. Rarely, chorea has occurred as a manifestation of rejection following cardiac transplantation. It is usually steroid responsive.

Neuromuscular problems

Mononeuropathies follow surgery and anaesthesia and may occur as a consequence of positioning, traction or the mechanical complications of surgery. Phrenic nerve damage can follow cold plegia of the heart (induced hypothermia) during cardiac transplantation. Rarely, systemic infection may lead to a form of polymyositis.

Acute myopathy sometimes follows liver transplantation, particularly in those receiving intravenous steroids and neuromuscular blocking agents. In general, the prognosis for neuromuscular complications following most transplantation is good providing there is no major structural damage, but this is not true for graft versus host disease (GvHD, see below).

Complications related to specific allograft transplantation

Renal transplantation

Renal transplantation is now undertaken routinely but neurological complications remain relatively frequent. Uraemic encephalopathy can develop suddenly following acute tubular necrosis, acute accelerated rejection or renal vein thrombosis. Spinal cord ischaemia may occur when the iliac artery is diverted for graft re-vascularization; this is a particular risk when there is an anomalous vascular supply to the spinal cord from the internal iliac artery rather than the intercostals. There is an increased frequency of cerebrovascular disease related to the underlying vasculopathy and hypertension, particularly in the presence of diabetes or systemic lupus erythematosus (SLE). However, there is evidence that combined kidney and pancreas transplantation decreases the subsequent incidence of stroke in diabetic patients. Compressive neuropathies involving the femoral nerve are often related to haematoma formation. Rejection encephalopathy is extremely rare.

Liver transplantation

Liver transplantation carries a relatively high incidence of complications. These may be related to the underlying hepatic disease including viral hepatitis, alcoholic liver disease, primary biliary cirrhosis, acute liver failure or toxic hepatic damage. Patients with hepatic encephalopathy have usually been critically ill and carry all the consequences of their underlying disorders following surgery. Delayed rejection or failing graft function may lead to recurrent encephalopathy or central pontine myelinolysis, impairment of coagulation and failure of synthetic and metabolic hepatic functions. Encephalopathy is also a common complication – associated with drug toxicity, metabolic derangement, hypoxic ischaemic injury and sepsis. Coagulopathies may also lead to intracerebral or subarachnoid haemorrhage. The postoperative period is frequently complicated by the development of severe sepsis.

Cardiac transplantation

Cardiac transplantation complications are usually related to bypass. Cannulation of the diseased ascending aorta may dislodge atheromatous material leading to cerebral emboli and there is a risk of introducing air emboli when bypass is discontinued. There remains a significant instance of ischaemic and haemorrhagic stroke, ischaemic hypoxic brain injury, encephalopathy and peripheral nerve injury often affecting the lower brachial plexus because of stretching during chest wall retraction. The recurrent laryngeal nerve may also be damaged leading to vocal cord paralysis; phrenic nerve paralysis, from direct trauma or cold plegia, can cause diaphragmatic weakness.

Lung transplantation

Lung transplantation is often undertaken in combination with heart transplantation. The complications are similar. Encephalopathy is usually a result of metabolic causes, drug toxicity or seizures. The cerebrovascular and neuromuscular complications are similar to those described above.

Bone marrow transplantation

Bone marrow transplantation is now widely undertaken both for the treatment of haematological malignancies but also as an adjunct in the treatment of other malignancies or autoimmune disorders. Neurological complications usually occur after allogenic bone marrow transplant requiring immunosuppression. Following bone marrow infusion, pancytopenia may be present for 2–5 weeks before a significant response is mounted. During this critical period, overwhelming Gram-negative sepsis, severe bleeding from thrombocytopenia and disseminated intravascular coagulation are the most serious complications. Transplantation is combined with radiotherapy or intrathecal chemotherapy. There may be an associated posterior reversible leucoencephalopathy. However, the most serious complication is the development of GvHD.

Acute GvHD occurs in the first 100 days following transplantation and primarily affects the skin, liver and intestines. Chronic GvHD is a different entity and may develop at any time later than 80 days following transplantation. The condition strongly resembles a vasculitic syndrome with scleroderma-like skin involvement, bronchiolitis, Sjögren's syndrome, polymyositis, myasthenia gravis and neuropathy.

Polymyositis may develop up to 4–5 years after allogenic bone marrow transplantation in association with GvHD. Seropositive myasthenia occurs sometimes with severe bulbar and respiratory muscle weakness. The use of neuromuscular blocking agents may lead to prolonged blockade and the development of critical illness myopathy. Acute demyelinating neuropathy has also been described in chronic GvHD. Reduction of immunosuppression usually results in improvement of the symptoms but there remains a high morbidity and mortality associated with the condition.

Neurological involvement in systemic vasculitides and related disorders

Neurological involvement in systemic vasculitic disorders is common although, with the exception of giant cell arteritis (GCA) and isolated cerebral angiitis (ICA), it is rare for patients with this group of disorders to present solely with neurological symptoms. As such, many neurological episodes occur in patients who already have an established rheumatological or systemic vasculitis diagnosis and who may consequently be receiving some form of immunomodulatory therapy. Neurological symptoms presenting in such patients can be split into three broad aetiological groups, each suggesting different therapeutic considerations. First, neurological symptoms or signs may develop with increased underlying systemic disease activity, needing prompt escalation of the immunomodulatory therapy. Second, the symptoms may be iatrogenic and related to side effects of disease modifying or other agents, e.g. a proximal myopathy associated with steroid therapy or reversible posterior leucoencephalopathy associated with immunomodulatory treatments. Third, the symptoms may be caused by a separate, and possibly associated disease process which requires attention on its own merits, e.g. ischaemic stroke in a patient with rheumatoid arthritis (RA) and diabetes.

Any part of the nervous system can be affected by the diseases described here, but the propensities vary across these conditions as do the causative mechanisms. For each disease mentioned below, the different sites of neurological involvement are ranked depending on how commonly they occur. Many of the disease mechanisms, and thus related therapeutic considerations are shared across these conditions and will be discussed first.

Pathological mechanisms

Regardless of the lesion site within the neuraxis, the final common pathway of vasculitis is ischaemic damage to neural tissue, usually with permanent damage. Histological examination of tissue from both the central and peripheral nervous systems often reveals a necrotizing arteritis affecting blood vessels with a transmural infiltrate initially consisting of a variety of reactive leucocytes, typically a mixture of polymorphs, lymphocytes and eosinophils. The proportions, subtypes and behaviour of these cells vary both within and across the different types of systemic vasculitides, with granulomas (a nodular aggregation of mononuclear inflammatory cells or modified macrophages usually surrounded by a rim of lymphocytes) more common in Wegener's granulomatosis (WG) and GCA. The cell populations at the lesion site also vary with the age of the lesion – neutrophils in the acute phase and intimal proliferation and fibrosis in the chronic phase. All these cellular responses conspire to reduce blood flow through the affected vessel. When individual nerves are involved the arteritis usually affects the pre-capillary arteries. In the CNS the calibre of blood vessel affected is associated with disease type, but overlaps are common. A nosology based primarily on vessel size is desirable but problematic, especially as immunotherapy is not yet at the stage where different populations of inflammatory cells can be targeted.

With inflammatory and reactive stromal cells narrowing the arterial lumen, secondary thrombotic events can occur causing distal embolism to terminal portions of the arterial tree. However, in some systemic disorders the vasculopathy may be primarily or even solely caused by thrombotic occlusion of arteries, capillaries or veins, in which case anticoagulation may be appropriate (see SLE, below). Other causes of secondary vasculitis affecting the nervous system, although not covered in any detail here include:

- *Infections:* fungi, TB, other bacteria, spirochaetes, viruses including VZV, HIV;
- *Drugs:* amphetamine, cocaine;
- *Malignancy:* either via direct involvement such as in lymphoma or as part of a paraneoplastic vasculitis.

Isolated cerebral angiitis (ICA) is a rare but well-recognized disorder. The existence of its peripheral equivalent, isolated peripheral nervous system vasculitis, is moot – with the majority opinion that all vasculitic neuropathies are secondary to an underlying disease, although it may take months or years for this to emerge (e.g. Sjögren's syndrome, below).

Compressive spinal cord or root pathology can occur in any of the systemic disorders, especially as steroid-related osteopenia has a predilection for the vertebral bodies. However, this is most commonly seen in patients with RA. Entrapment neuropathies can be caused by nodule formation in RA (typically ulnar or median nerve) or granulomas (typically cranial nerves). Ophthalmoplegia occurs in approximately 5% of patients with WG. The cause of this may be varied or indeed multifactorial:

- Contiguous extension of a granulomatous mass from a nasal or paranasal site into the orbit causing pseudotumour;
- Vasculitis of the extraocular muscles;
- Oculomotor palsy secondary to vasculitis; or
- Granulomatous compression at some point along a cranial nerve.

Dedicated MRI scanning protocols with contrast may help demonstrate the cause.

Diagnosis and treatment of vasculitides involving the nervous system

Because immunosuppressive therapies for vasculitis are relatively toxic, the decision to administer them should be supported by a tissue diagnosis, if at all possible. When neurological symptoms and signs occur alongside multi-system disease activity, a diagnostic biopsy may well be from affected skin, kidney or lung. However, if the neurological syndrome occurs while disease remains quiescent in other organs then brain, nerve or muscle biopsy may be the only reasonable option.

Immunosuppressive treatment of neurological involvement in systemic disorders is unlikely to be based directly on prospective randomized trials; however, indirect evidence is available from controlled trails of patients with systemic vasculitis. Given that the underlying pathology is similar in non-neurological organs, extrapolation is reasonable. In general, the majority of vasculitic disorders can be reversed or controlled in some 90% of patients with a combination of high-dose oral corticosteroids and oral cyclophosphamide. Cyclophosphamide is usually given for 3 months with less toxic drugs such as azathioprine to sustain remission while steroid therapy is gradually reduced. Newer agents or non-pharmacological treatments such as plasma exchange may need to be used in resistant or persistently relapsing conditions. Many of the current immunosuppressive drugs and their associated side-effect monitoring parameters are included in Table 25.4.

Polyarteritis nodosa and related conditions

Polyarteritis nodosa (PAN) is the prototype necrotizing vasculitis. Medium-sized vessels are those usually affected and can be associated with aneurysm formation, seen on angiography. Middle-aged men are most commonly affected. Systemic symptoms include abdominal pain (from hepatic or other visceral infarcts), hypertension (from renal involvement, although glomerulonephritis is

Table 25.4 Drug treatments for vasculitis.

Drug	Class/action	Side-effects	Monitor (prophylaxis)
Acute, induction or rescue therapy			
Methylprednisolone	Corticosteroid	Diabetes, neuropsychiatric, hypotension	Glucose, BP
Cyclophosphamide	Alkylating agent	Haemorrhagic cystitis, bone marrow suppression, neutropenia, sepsis	FBC (mesna for cystitis)
IVIG	Pooled antibodies from ~1000 human donors	As for any blood product, renal failure rarely	Check IgA levels before therapy, (absent IgA = absolute contraindication), U+E
Infliximab	Monoclonal anti-TNF antibody	Hypersensitivity (delayed), atypical infections especially TB, induction of dsDNA antibodies	FBC, U+E, LFTs. CXR (exclude TB), ANA and dsDNA. Use prophylactic isoniazid in patients at high risk for TB
Rituximab	Monoclonal anti-CD20 antibody	Infusion related	FBC, B lymphocytes
Long-term therapy			
Prednisolone	Corticosteorid	Diabetes, osteopenia, adrenal suppression	DEXA scan (bisphosphanates for osteoprophylaxis)
Mycophenolate mofetil	Inhibitor of inosine monophosphate dehydrogenase	Bone marrow suppression, gastrointestinal intolerance, chronic viral infections	FBC; (ideally) monitor mycophenolic acid levels
Methotrexate	Folate antagonist/adenosine agonist	Pulmonary fibrosis, liver failure, bone marrow suppression	FBC, U+E, LFT (folate prophylaxis)
Azathioprine	Blocks purine synthesis	Bone marrow suppression, squamous-cell carcinoma, chronic viral infections, hypersensitivity	FBC + (ideally) check thiopurine methyltranferase (TMPT) pre-Rx. (absent TMPT = absolute contraindication; reduced level = reduce dose)
Tacrolimus	Calcineurin inhibitor	Diabetes, hypertension	FBC, U+E, glucose, tacrolimus levels

IVIG, intravenous immunoglobulin; TNF, tumour necrosis factor.

not a feature), fever and weight loss. Diagnosis is based on the clinical features and either positive angiography or biopsy of affected tissue (skin, kidney or nerve). The only serological marker clearly associated with PAN is hepatitis B infection (20–40% HbsAg-positive). PAN is considered to be an antineutrophil cytoplasmic autoantibodies (ANCA)-negative syndrome.

The most common neurological problem is a progressive mononeuritis multiplex (MNM) which occurs in up to 50% of patients with PAN. In common with other causes of vasculitic mononeuritis this tends to present with a painful sensory or sensorimotor picture. More central involvement occurs in 25% of cases, in a variety of patterns – encephalopathy, seizures, stroke, aseptic meningitis, rarely an ischaemic myelopathy and sometimes cranial nerves palsies.

Microscopic polyangiitis (MPA) is related to PAN and is also more commonly seen in males. Unlike PAN, the kidneys are most commonly affected and when the lungs are simultaneously involved it is one of the causes of 'pulmonary–renal syndrome', along with WG, SLE, Churg–Strauss and Goodpasture's syndromes. Other less specific features include arthralgia, purpuric rashes, myalgia and conjunctival haemorrhage. Like PAN, diagnosis rests primarily on the clinical syndrome with histological support from affected tissue (usually kidney skin or lung). Angiography has less of a role in MPA because, as its name suggests, it tends to affect arterioles, capillaries or venules below the resolution of direct angiography. MPA, like WG, is associated with circulating ANCA. There are two main ANCA staining patterns, perinuclear (pANCA) associated with the myeloperoxidase antigen, and cytoplasmic (cANCA), associated with the neutrophil enzyme proteinase 3. Both these forms are seen in microscopic polyangiitis (60–70% pANCA and 30–40% cANCA); combined they have a sensitivity of 90% with a specificity of 70%. ANCA can also be positive in RA and SLE patients. The pattern of neurological involvement seen in MPA is similar to that of PAN.

Like MPA, Churg–Strauss syndrome (CSS) affects the lungs and kidneys and also has an association with ANCA, albeit a weaker one. Unlike other systemic vasculitides, CSS produces symptoms of asthma and is almost always associated with a peripheral eosinophilia ($>1.5 \times 10^9\,L^{-1}$). Cardiac, gastrointestinal and skin involvement is also common. Histology of affected tissue usually shows three cardinal features: necrotizing vasculitis, granulomas and infiltration by eosinophils. Typically, a vasculitic neuropathy is seen in CSS and sometimes with WG and MPA.

Wegener's granulomatosis

WG is characterized by the triad of upper respiratory tract granuloma (typically affecting the nasal mucosa and/or inner ear), lower respiratory tract granuloma (typically pulmonary nodules) and a necrotizing glomerulonephritis. Non-specific generalized skin and joint symptoms akin to those described for MPA also occur. cANCA is usually found in this condition and has a specificity of 95% and a sensitivity of 80%. Some physicians use circulating levels as an indirect disease marker against which immunomodulatory therapy can be titrated.

The best data for neurological complications associated with WG come from a large series from the Mayo Clinic, of over 300 cases. Patients rarely died of neurological complications, but one-third had neurological involvement at one or more sites in the nervous system at some point in their illness:

- Peripheral polyneuropathy 50%;
- Cranial neuropathy, including hearing loss 20%;
- Ophthalmoplegia 15%;
- Stroke 12%;
- Seizures 10%; and
- Cerebritis 5%.

Peripheral nerve involvement is heavily skewed towards mononeuritis multiplex (80% of neuropathy patients) with 10% having an insidious distal symmetrical polyneuropathy; a further 10% were unclassified. The most common nerve affected by mononeuritis multiplex is the common peroneal nerve, followed by the tibial, ulnar, median, radial and femoral nerves. Fifty per cent of those with cranial nerve involvement have optic nerve pathology, usually an arteritic anterior ischaemic optic neuropathy. Cranial nerves VI and VII were the next most commonly affected. Ophthalmoplegia can be the presenting symptom in WG, and may be caused by several mechanisms. All call for an increase in immunomodulatory therapy. Acute or subacute hearing loss is associated with WG; this is often because of a combination of conduction hearing loss (otitis media or otitis interna) and sensorineural loss (granuloma or vasculitic processes affecting the auditory nerve).

Sjögren's syndrome

Sjögren's syndrome (SS) is characterized by lymphocytic infiltrates and destruction of epithelial exocrine glands. The main symptoms are dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia). SS is classified as primary (where dry eyes and dry mouth with systemic complications are more common), or secondary to other connective tissue disorders such as RA, SLE or overlap syndromes (mixed connective tissue diseases [MCTD]; see below). Systemic involvement is characterized by chronic fatigue, arthralgia, oesophageal hypomotility, haematological disorders and rarely a cutaneous vasculitis, alopecia and vitiligo.

The primary syndrome usually affects females (9 : 1 female : male ratio), develops slowly and is associated with B-cell lymphoma in 5% of cases. Lymphocytic infiltration may lead to cutaneous purpura, lymphocytic alveolitis/interstitial pneumonitis and malabsorption. There may also be a renal tubular necrosis, nephritis and Raynaud syndrome. Antinuclear antibodies, rheumatoid factor and various ENAs (anti-extractable nuclear antigen antibodies, specifically anti-Ro and anti-La antibodies) are associated with SS; Schirmer's test for objective evidence of dry eyes and minor salivary gland biopsy showing focal lymphocytic sialadenitis (usually of the lip) also have a role in the most recent diagnostic criteria.

In SS several different types of neuropathy have been described; the most common pattern (approximately 50%) is of an asymmetric, segmental or multifocal sensory neuropathy starting with distal parasthesia but often progressing to involve the trunk or face. A large proportion of these patients have an associated sensory ataxia, severe in some cases; they are likely to have high signal intensity in the posterior columns of the spinal cord on T2 MRI. In some subjects, ataxia is less prominent but neuropathic pain more so; the general progression of symptoms tends to be over months to years. A less common pattern of peripheral nerve involvement is one of a sensory and motor syndrome indistinguishable from mononeuritis multiplex (MNM) seen in other connective tissue disorders; the progression tends to be acute or subacute rather than slowly progressive. Neuropathological studies suggest that the sensory–ataxic pattern is caused by a ganglioneuronitis with lymphocytic infiltration of the dorsal root ganglia similar to that seen in the glandular tissues of the mouth. While a vasculitic pathology is more likely to underlie the MNM type, overlap forms clearly occur.

Cranial neuropathies are also associated with SS and again tend to follow one of two patterns mirroring involvement of the peripheral nerves: either a sensory neuropathy affecting one or both trigeminal nerves with no motor features, or a cranial polyneuropathy that can affect any nerve with little discrimination between motor and sensory nerve populations. Hearing loss is sensorineural because of a lesion of the VIIIth nerve and this may develop suddenly or progressively. Autonomic features are often associated with SS neuropathies (60%): abnormalities of pupillary function (Holmes–Adie pupils), sweating and orthostatic hypotension are the most common manifestations; a pure autonomic neuropathy also occurs, but is much rarer. Many older patients who are diagnosed with SS turn out to have had a chronic, apparently idiopathic, neuropathy for many years, so it is worth screening for SS in this group, especially if the symptoms are patchy or associated with autonomic features.

CNS involvement is increasingly recognized and may be severe. MS-like features are often associated with a cutaneous vasculitis and optic neuropathy. Other manifestations include meningo-encephalitis with stroke-like episodes, intracerebral or subarachnoid haemorrhage resulting from vasculitis and focal abnormalities including sensorineural deafness, internuclear ophthalmoplegia, nystagmus, dystonia, athetosis, parkinsonism, focal and generalized seizures. Rarely, affective symptoms may develop as a consequence of an encephalopathic-like presentation with depression, anxiety and cognitive impairment. Spinal cord involvement can develop with an acute transverse myelitis of sudden onset, usually associated with a vasculitis; more progressive forms of spinal cord involvement may also occur. The MRI changes are of focal high signal abnormalities on T2 images in the brain white matter and cortex and in the spinal cord. These can be indistinguishable from those seen in MS.

If there is involvement of the peripheral or central nervous system, aggressive treatment for underlying vasculitis is indicated. The first line is with intravenous corticosteroid therapy but if progression continues an alternative immunosuppressant may be indicated. The sensory axonal ganglioneuropathy responds poorly to immunosuppression. Other agents that may augment steroids include azathioprine and hydroxychloroquine.

Rheumatoid arthritis

RA, also known as rheumatoid disease, is a multisystem disorder usually presenting with a symmetrical distal polyarthropathy. Stiffness of the joints is usually prominent, especially in the morning and the diagnosis is usually supported by the presence of rheumatoid nodules, positive rheumatoid factor in serum and characteristic juxta-articular changes on X-rays of affected joints. Inflammatory or vasculitic neurological complications also occur but are rare. More common are entrapment neuropathies and, most worrying, spinal cord or lower brainstem syndromes secondary to erosive skeletal involvement of the atlanto-axial, odontoid or other vertebral components. The cervical spine is most often affected by erosive disease but extradural pannus can cause compression at any spinal location, including the cauda equina.

A group of rheumatological disorders overlap with RA, the mixed connective tissue diseases (MCTD) consisting of RA, scleroderma, SS, SLE and myositis. Patients with this disorder are often positive for the U1-RNP antibody which is associated with the main threat to life: pulmonary hypertension. Neurological manifestations are similar to those seen in RA or SLE; an inflammatory myopathy is present in up to 50% of cases. Evidence suggests that MCTD-associated myopathy is particularly responsive to steroids.

Systemic lupus erythematosus

SLE is a multi-system disorder like RA, which commonly affects the joints and almost any other organ system, although the arthritis is less erosive than that seen in RA and mucocutaneous involvement more common. Antinuclear antibodies (ANA) are often present in SLE, but the test has a high false positive rate and detection of more specific antibodies to intracellular antigens is often required (e.g. double and single stranded DNA). Neurological complications of SLE usually occur within the CNS. In the largest unselected cohort to date, up to 50% had so-called neuropsychiatric lupus (NPSLE). This proportion is closer to 30% if all those with headache alone are excluded, as they probably should be because headache is no more common in SLE patients than controls. Mood disorders, strokes and cognitive disorders all occur in 10–15% of patients; seizures, frank psychosis and acute confusional states are less common, as are disorders of the nerve or muscle.

The exact mechanism(s) involved in NPSLE are still unclear. The current evidence favours a primary thrombotic/occlusive cerebral vasculopathy over a vasculitis, with antiphospholipid antibodies, particularly those directed at cardiolipin, present in 55% of patients with NPSLE compared to 20% with SLE alone. The therapeutic implication is that NPSLE should be treated with anticoagulation rather than immunosuppressive therapy.

Isolated cerebral angiitis

ICA or primary cerebral vasculitis is especially difficult to diagnose. Unlike most of the diseases mentioned above, there are neither extra diagnostic clues from involvement of non-neurological organ systems, nor specific serological nor CSF tests. ICA can present in a wide variety of ways with an acute or subacute, relapsing or even chronic time course. Three main patterns of presentation are proposed: an encephalopathic picture with accompanying headache, confusion and coma; isolated or multiple intracranial mass lesions with a mixture of focal and general CNS signs and raised ICP; an atypical MS-like syndrome with a relapsing-remitting course, optic nerve involvement, sometimes with stroke-like episodes and seizures.

Although brain MRI is usually abnormal in patients with ICA, there are no pathognomic findings; intra-arterial cerebral angiograms have a disappointing specificity and sensitivity, of the order of 30%. This leaves brain biopsy as the diagnostic test of choice. Brain biopsy (including meninges) leads to a diagnosis in over 75% of cases, even when targeted at radiologically normal looking brain tissue. However, about half of positive biopsies for presumed ICA show an alternative, unsuspected cause of the problem. Infection, lymphoma and MS are high on this list.

Treatment of ICA is not and may never be based on prospective placebo-controlled trials. However, as with treatment for the systemic vasculitides, more potent immunosuppression than can be provided by steroids alone is almost certainly warranted. A current reasonable therapy regimen would be: intravenous methylprednisolone 1 g/day for 3 days followed by 60 mg/day prednisolone tapering over months and eventually being superseded by a steroid-sparing agent such as azathioprine, with oral cyclophosphamide 2 mg/kg/day for 9–12 weeks, starting after the 3 days of intravenous steroid.

Giant cell arteritis

GCA, widely known as temporal arteritis, is the most common primary vasculitis affecting those over 50 years. Typically, the extracranial branches of the aorta and the aorta itself are involved, with intracranial involvement much more rarely, probably because intracranial vessels lack the internal elastic lamina that appears to be the focus of the inflammatory response. Headache is the most common symptom, but can be absent. Other symptoms caused by involvement of extracranial arteries include jaw claudication and scalp tenderness. Constitutional symptoms are present in at least one-third of cases as this condition overlaps with polymyalgia rheumatica (weight loss, fever and myalgia). Blindness is the most common serious neurological sequel and can present with either monocular (or bilateral) or homonymous visual loss. The former is caused by arteritic involvement of the posterior ciliary arteries, leading to optic nerve head infarction which may be partial causing sector or altitudinal field defects. The latter is caused by thrombo-embolism of the posterior cerebral arteries, which are preferentially affected. Sequential ischaemic optic neuropathies or bilateral occipital infarction can lead to permanent blindness. Strokes affecting the MCA territory also occur, although they are rarer. Sometimes the arteritis is clinically apparent to palpation. Affected arteries feel thickened, pulseless and cord-like, such as the superficial temporal artery or other extracranial branches of the external carotid artery, the facial artery as it runs under the mandible, or the occipital arteries as they run over the inion. The ESR is almost always raised as is the CRP; anaemia is present in two-thirds of cases with a leucocytosis and raised transaminases in one-third. Temporal artery biopsy is the most specific finding but often a diagnosis will have to be made without this confirmation as skip lesions occur. The diagnostic yield drops with the interval following initiation of steroid therapy, although this fact should not delay initiating steroids;. perusing a biopsy after the oft-quoted two week window of opportunity post-steroids is occasionally fruitful. Patients started on steroids are not completely protected from ischaemic events; there is good evidence for starting patients also on low-dose aspirin when GCA is suspected.

Miscellaneous cerebral arteriopathies

CADASIL

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy) is an autosomal dominant disease of small cerebral vessels caused by mutations in the *notch 3* gene on chromosome 19q13. *Notch 3* is a large gene coding for a transmembrane protein involved in intracellular signalling. The condition is characterized by episodic migraine-like headaches and recurrent subcortical ischaemic strokes usually beginning in mid-adulthood. A multifocal motor and sensory deficit develops often with cognitive impairment, incoordination and progression to pseudobulbar palsy and subcortical dementia (Chapter 7).

Imaging with CT or MRI shows confluent white matter disease and multiple small deep infarcts with myelin loss usually sparing the U fibres (Figure 25.6 and Figure 7.8). White matter change characteristically involves the anterior temporal horn and external capsule, areas that are less frequently affected in sporadic cerebral small vessel disease. Genetic testing for *Notch 3* mutations allows non-invasive confirmation of the diagnosis in many

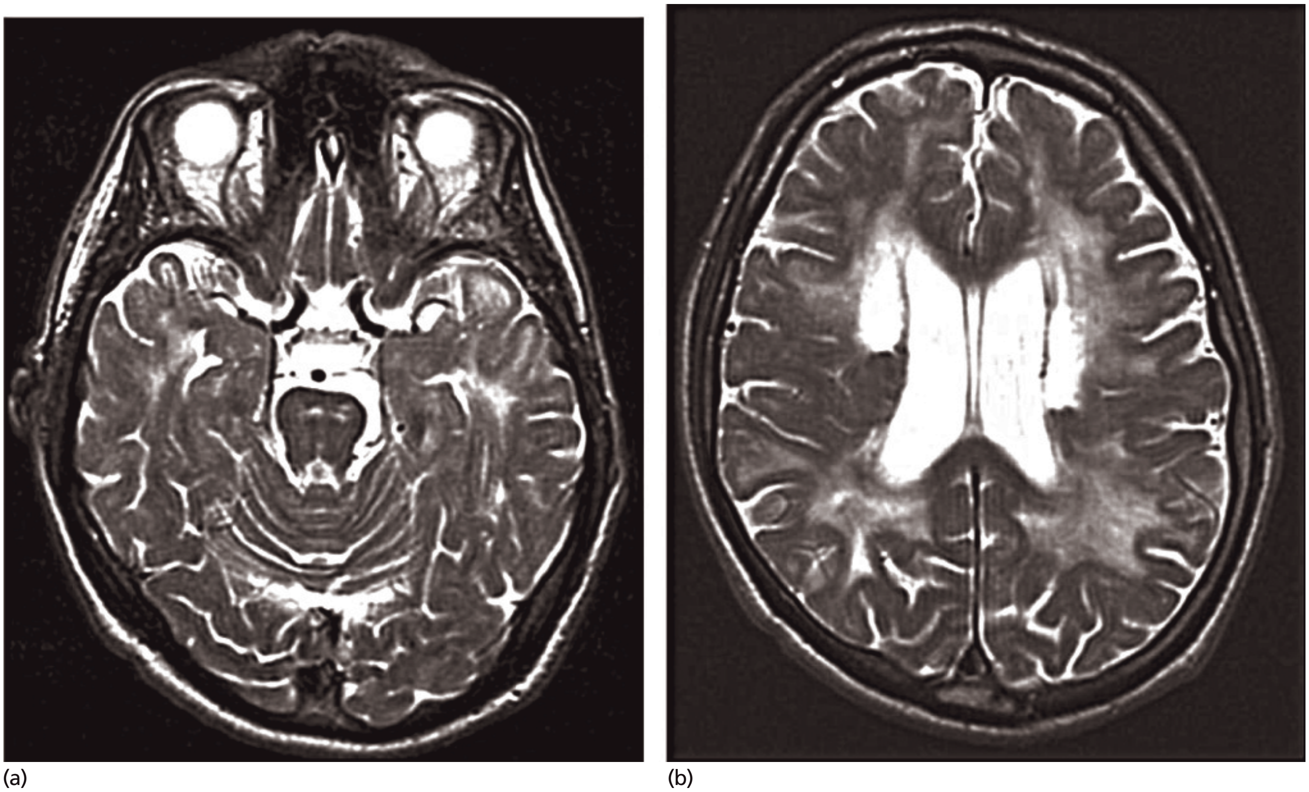
(a) (b)

Figure 25.6 CADASIL. T2 axial MRI from a 54-year-old man with recurrent migraine, TIAs and subcortical stroke syndromes and progressive cognitive impairment. Note the high signal in both anterior temporal lobes, extensive and confluent high signal in the deep cerebral white matter, and bilateral subcortical infarcts. Genetic testing confirmed the diagnosis of CADASIL.

cases. Skin biopsy reveals pathological changes of a non-amyloid angiopathy with deposition of eosinophilic electron dense granular material within the media of the small arteries and arterioles. This leads to concentric arterial wall thickening, narrowing of the vessel lumen and impaired reactivity of the vessel culminating in chronic arterial insufficiency, ischaemia and infarction.

The prognosis for CADASIL is poor with progressive stepwise deterioration leading to severe impairment of sensory and motor function and progressive dementia. However, recent data suggest that treatment of modifiable vascular risk factors including hypertension, lipid abnormalities and hyperhomocysteinaemia is appropriate and may limit the severity of phenotypic expression of the disease.

Fabry's disease

This important, potentially treatable disease is discussed in Chapters 4 and 18.

Susac's syndrome

Susac's syndrome is a micro-angiopathy of unknown aetiology affecting the brain, cochlea and retina and manifests as a triad of encephalopathy, sensorineural hearing loss and branch retinal artery occlusion. The condition predominantly affects women. At presentation not all of the clinical triad may be present. The onset of encephalopathy is typically associated with prodromal headache that may last for several months before the development of cognitive and psychiatric symptoms, sometimes with seizures and myoclonus. The hearing loss is often acute, bilateral and symmetrical suggesting infarction because of occlusion of the cochlear end arteries. Sometimes hearing loss is asymmetric or even asymptomatic, being detectable only on audiometry. Visual loss is characteristically segmental, and fundoscopy reveals multiple branch retinal artery occlusions and a macular cherry red spot. The EEG shows diffuse encephalopathic changes and MRI confirms multiple small high signal white matter lesions on T2 imaging typically involving the corpus callosum, and sometimes the posterior fossa and brain parenchyma. CSF shows elevated protein with normal cells or a minimal pleocytosis; oligoclonal bands are absent. Histological changes on brain biopsy confirm micro-infarcts resulting from arteriolar occlusion but the mechanism is unclear as there is neither vasculitis nor fibrinoid necrosis. There is no clear guidance to treatment particularly given the tendency for spontaneous remission. The rarity of the condition precludes clinical trials. Antiplatelet agents and steroids are widely used and second line immunosuppression with cyclophosphamide and azathioprine has been recommended. Rarely, plasma exchange and intravenous immunoglobulin have been used.

Sneddon's syndrome

Sneddon's syndrome is a rare disorder characterized by recurrent strokes (typically in the middle cerebral artery territory) in young patients, often with a history of migraine. Cognitive impairment may develop. There is livedo reticularis (a fixed violaceous and net-like rash on the limbs and trunk); antiphospholipid antibodies may be elevated. The pathology is of an arteriopathy affecting small and medium-sized vessels. Some MRI studies have shown extensive cortical high signal lesions and atrophy. The condition is associated with antiendothelial cell and antiprothrombin antibodies. Treatment is of standard vascular risk factors including hypertension. Anticoagulation may be considered, particularly in the presence of antiphospholipid antibodies.

Degos disease

Degos disease is a multi-system small vessel occlusive arteriopathy leading to ischaemia, initially involving the skin causing erythematous pink or red papules which heal to leave scars with characteristic white atrophic centres. Gastrointestinal and CNS complications may develop as the disease progresses. Ischaemic and haemorrhagic stroke may occur in the absence of vasculitis. Neurological involvement is characterized by the development of paraesthesiae, visual symptoms, weakness and myelopathy. MRI may demonstrate multi-focal ischaemic abnormalities or dural enhancement; skin biopsy shows vasculopathy but no active vasculitis.

Sarcoidosis

Sarcoidosis is a multi-system granulomatous disorder of unknown aetiology that affects the nervous system in some 5% of patients. Its hallmarks are non-caseating epitheloid cell granulomas with associated inflammation and the development of secondary fibrotic change which causes irreversible tissue damage.

Clinical features and investigation

The clinical presentation depends upon the pattern of organ involvement. Systemic sarcoid affects the lungs in 90% of patients; involvement may vary from bilateral hilar lymphadenopathy to severe interstitial lung disease. Other organs often involved include the liver, lymph nodes, skin, endocrine and musculoskeletal system. The diagnosis in the presence of hilar lymphadenopathy may be confirmed by bronchoscopy, broncho-alveolar lavage or tissue biopsy. The presence of elevated serum angiotensin-converting enzyme (SACE) and characteristic imaging appearances may help but have limited specificity. CSF ACE may be elevated. Gallium scans may show characteristic increased uptake in parotid salivary glands. However, in the absence of tissue evidence of non-caseating granulomas the diagnosis may be extremely difficult and is often one of exclusion. Acute presentation is associated with a good prognosis but poorer prognostic features include a later age of onset, Afro-Caribbean extraction, the presence of lupus pernio, chronic uveitis, chronic hypercalcaemia, progressive pulmonary pathology, nasal mucosal disease or cardiac involvement. Neurological involvement is uncommon but carries a worse prognosis than pulmonary disease and may be associated with ocular and cardiac involvement. In approximately 15% of patients with neurosarcoidosis the presenting features are neurological but in others neurological involvement develops within 2 years of presentation. Chronic neurosarcoidosis can cause multiple cranial nerve palsies, parenchymatous cerebral involvement, hydrocephalus and encephalopathy or peripheral nervous system manifestations.

Cranial neuropathy

The most common neurological manifestations are isolated cranial neuropathy or aseptic meningitis. Up to 75% of neurosarcoid patients present with an isolated or bilateral facial palsy. This may be associated with dysgeusia, indicating a proximal lesion affecting the chorda tympani. Deafness from VIIIth nerve involvement occurs in 10–20% of cases; bilateral involvement strongly suggests neurosarcoidosis. Optic neuropathy occurs in up to 40% of patients and is often subacute, presenting with a progressive visual field defect, impaired acuity and pupillary dysfunction. Examination may show anterior uveitis, papillitis, papilloedema or optic atrophy secondary to granulomatous infiltration or compression of the optic nerve. Oculomotor abnormalities or bulbar weakness may occur as a result of a diffuse meningeal infiltration. Infiltration is common at the base of the brain and may lead to hydrocephalus in 6–30% of neurosarcoidosis patients which may be either obstructive or communicating. CSF diversion procedures may be necessary but tend to fail.

Meningeal and parenchymatous sarcoid

Meningeal involvement commonly presents as an aseptic meningitis or occasionally as a meningeal mass lesion. The CSF shows a mononuclear pleocytosis with an elevated protein and a reduced glucose level. Parenchymal lesions are unusual. Clinical manifestations depend on their location and size. They can mimic tumours or demyelination, cause raised intracranial pressure with headache and papilloedema, seizures or focal involvement of the brainstem, basal ganglia or cerebellum. Isolated spinal lesions may present as a progressive myelopathy with paraparesis and sphincter dysfunction. Pituitary and hypothalamic involvement occurs and can result in neuroendocrine disorders including diabetes insipidus, pan-hypopituitarism and hyperprolactinaemia.

Sarcoid encephalopathy

A diffuse or relapsing sarcoid encephalopathy may present with cognitive impairment or a confusional state often associated with memory disturbance. T2 MRI shows diffuse contrast enhancement of the meninges with increased signal. Encephalopathy may coexist with a diffuse vasculopathy characterized by arteritis, external compression of arteries by an inflammatory mass lesion or multiple cardiac emboli. Rarely, dural venous thrombosis may occur. Neuropsychiatric features are also well described, presenting with psychosis or bipolar affective disorder. There may occasionally be an isolated progressive amnesia or dementia without evidence of other neurological or systemic involvement. These patients appear to respond well to steroids.

Peripheral neuromuscular sarcoid

Peripheral neuromuscular involvement occurs in some 20% of patients with neurosarcoidosis. Peripheral nerve involvement may be either an isolated mononeuritis, or a mononeuritis multiplex caused by granulomatous vasculitis or compression from granulomas. A symmetrical chronic axonal neuropathy occurs in some 25% of neurosarcoid patients. This is usually mild and of a mixed sensorimotor pattern but a more acute form indistinguishable from Guillain–Barré syndrome with demyelinating features may also develop. Muscle involvement is common but usually asymptomatic with non-caseating granulomas found on biopsy in more than 25% of patients. Symptomatic involvement varies from acute to chronic myopathy with an inflammatory component and occasionally palpable intramuscular nodules.

Diagnosis

Diagnosis can be challenging; histological confirmation should be sought if possible. MRI may show parenchymatous mass lesions – hyperintense lesions on T2 sequences, with linear enhancement of thickened meninges and focal nodular enhancement. CSF findings are non-specific but may be helpful if there is meningeal involvement. There may be a pleocytosis of up to 100 cells/mm² and elevated protein <2 g/dL (occasionally higher). Glucose is also occasionally reduced in active aseptic meningitis, CSF pressure is increased and oligoclonal bands present variably. Muscle biopsy can be diagnostic. Biopsy of cerebral lesions and the meninges may be helpful, and the non-caseating granulomatous changes are diagnostic.

Prognosis

The prognosis is variable but generally neurosarcoidosis is a serious disease. Involvement of the peripheral nervous system tends to carry a better prognosis than central involvement. One-third of neurosarcoid cases have progressive disease despite immunosuppression with steroids and other agents.

Steroids are the principal treatment for neurosarcoidosis; the dose and duration are determined by the disease location severity and time course. Treatment aims to reduce the inflammatory component and prevent progression to fibrosis and ischaemia. Steroids should be built up rapidly to high doses and the dose tapered only after clinical response has been established. Occasionally it is possible to withdraw steroids completely but many patients require long-term steroids and some require additional immunosuppressive agents such as azathioprine, methotrexate, ciclosporin or mycophenolate.

Behçet’s syndrome

Behçet’s syndrome (BS), described by the Turkish dermatologist Professor Hulusi Behçet (1889–1948), is a multisystem disease consisting of recurrent oral ulceration (at least three times in a year) and two of the following: recurrent genital ulcers, skin lesions, ocular lesions and a positive pathergy test. Neurological involvement occurs in approximately 5% of cases and falls into two distinct patterns which rarely overlap:

Table 25.5 Multisystem manifestations of Behçet's syndrome.

Ocular (present in 70–95%) (loss of vision occurring approximately 3 years after onset of ocular symptoms)	Acute pan-uveitis usually associated with hypopyon Scleral and corneal involvement Conjunctival aphthous lesions Glaucoma Posterior segment changes Alteration in macular pigment epithelium Peri-venous sheathing Retinal and vitreous haemorrhages and exudates Occlusion of retinal arteries and veins Retinal detachment Optic and retrobulbar neuritis (becomes bilateral in 50% within 1 year and 80% within 2 years)
Mucocutaneous	Oral ulceration: small round oval painful crops on gums, lips, tongue, palette, posterior pharynx Genital ulcers: deep, painful and scarring Skin lesions: pustules, vesicles, folliculitis, acneiform lesions and erythema nodosum
Arthritis	Non-erosive, non-migrating, oligoarticular involvement of large joints especially knees, ankles and wrists
Gastrointestinal	Constipation, diarrhoea, abdominal pain and vomiting Ulcers may occur in any part of the gastrointestinal tract especially distal ileum and caecum
Vascular involvement	Arterial and venous malformations Venous – superficial thrombo-phlebitis, DVT, superior venocaval obstruction, Budd–Chiari syndrome and cerebral venous sinus thrombosis Arterial inflammatory change presenting as occlusion or aneurysm formation of the pulmonary, renal, subclavian, femoral and carotid arteries
Pulmonary	Recurrent haemoptysis, cough, chest pain and dyspnoea
Cardiac	Peri-myocarditis or endocarditis or coronary arteritis
Gastrointestinal	Dysphagia, epigastric pain, colicky abdominal pain and bloody diarrhoea

DVT, deep venous thrombosis.

- Parenchymal CNS lesions, most commonly affecting the brainstem, although any part of the CNS can be involved, known as neuro-Behçet's syndrome (NBS); and
- Cortical venous sinus thrombosis (CVST).

The former is associated with relapsing-remitting and progressive disease patterns often culminating in moderate or severe disability; the latter tends to occur as a single episode. Features of the multiple systems affected by BS are shown in Table 25.5.

Epidemiology and pathology

BS usually occurs in the third decade and is seen most commonly in regions along the ancient Silk Route, thus extending from the Eastern Mediterranean to Japan; the prevalence in Turkey and Japan is 20 times that in the UK. Men are more commonly affected than women (1.4 : 1), a ratio that rises to 3 : 1 when considering cases of NBS. HLA B51 is associated in 50% of patients with BS, especially those with uveitis.

There is still a debate whether or not the neuropathology of BS is primarily one of vasculitis. While active CNS lesions often contain perivascular inflammatory infiltrates, the arteriolar vessel wall itself is rarely involved; associated fibrinoid necrosis is not reported in CNS pathological specimens. Blood vessels with characteristic changes suggesting vasculitis have been encountered in non-CNS organs, but usually on the venous side of the circulation.

Patterns of nervous system involvement

Of patients with BS and neurological symptoms or signs other than isolated headache, roughly 80% present with NBS while the remaining 20% have CVST. Headache is the most common neurological symptom in BS, even given its high prevalence in the general population. Both migraine and tension-type patterns are seen. New or severe headache in patients with known BS should prompt imaging as CVST or parenchymal lesions will sometimes be found.

CNS involvement: parenchymal

The most common pattern of NBS is of a subacute brainstem syndrome that may be associated with lesions elsewhere in the CNS or, more rarely, cranial neuropathies (V, VII or VIII). Spinal cord and hemispheric presentations are also common. Symptoms not easily localizable are also seen (impaired consciousness, epilepsy, neuropsychiatric BS). Isolated optic neuropathy is rare (>1%), as are peripheral neuropathies. Most authors do not accept the existence of isolated NBS without pre-existing BS, arguing that those patients who present with neurological symptoms have a history of recurrent oral ulcers at least.

NBS can mimic a variety of disease states with MS being high on the differential list in Western practice. Although NBS can have a relapsing remitting or progressive course like MS, it is usually differentiated on the following grounds: MRI in NBS often reveals symptomatic lesion(s) below the tentorium, as opposed to the multiple, clinical silent, periventricular lesions commonly seen in MS. CSF protein and lymphocyte counts are similar in both disorders, but oligoclonal bands are either absent or matched with serum in NBS and, if present, disappear on remission, compared to the persistently present unpaired intrathecal oligoclonal bands found typically in MS. Optic neuritis is rare in NBS and when associated VEPs are abnormal, the pattern is of reduced amplitude and preserved latency rather than normal amplitude and prolonged latency encountered in demyelination. Lastly, systemic symptoms and headache are seldom present in an acute attack of MS.

Although NBS rarely complicates BS, parenchymal disease is sometimes a cause of major disability. 45% of patients with NBS have a single neurological episode, while half each of the remainder have either a relapsing-remitting or a progressive course. NBS is a serious disease: half of all NBS patients have an Expanded Disability Status Scale (EDSS) of >6 at 10 years from diagnosis.

Cerebral venous sinus thrombosis

Symptomatic CVST should be treated with anticoagulation (either low molecular weight heparin or warfarin) in the short to medium term and, given that it rarely recurs, long-term anticoagulation is not warranted. The main caveat to this statement is that BS in general and BS complicated by CVST in particular, are associated with coexisting pulmonary artery aneurysms (PAA). These aneurysms (which can occur at other sites in the vascular tree) are probably caused by inflammatory changes in the vasa vasorum of the larger pulmonary vessels, which can result in necrosis of the vessel wall causing true aneurysms or dissection causing false ones. It is prudent therefore to screen patients with BS and CVST for PAA (usually with a CT pulmonary angiogram), before starting anticoagulation. PAA in BS can be treated with immunosuppression, endovascular intervention or surgery.

Investigation

Peripheral blood is often but not always normal, with an absence of acute phase reactants. CSF examination shows pleocytosis (neutrophils and lymphocytes with an elevated protein but normal glucose). The opening pressure is increased if there is venous sinus thrombosis but oligoclonal bands are only present in a minority. The pathergy test is somewhat variable in its sensitivity. MRI in the acute stage may show lesions that appear iso- or hypo-intense on T1 images and hyper-intense on T2 and FLAIR, due to venous thrombosis with reversible oedema; lesions may be single or multiple. They are seen most commonly in the mesodiencephalic junction, cerebellar peduncle, basal ganglia and brainstem but can also occur in the optic nerve and hemispheres. In chronic disease brainstem atrophy with gliosis can develop.

Pathergy test in Behçet's disease

The forearm is pricked with a fine sterile needle. With a positive pathergy test, a small red bump at the site of needle insertion develops 1–2 days later. Histologically there is a largely lymphocytic reaction. Not all Behçet's cases have positive pathergy tests. Behçet's patients from the Mediterranean littoral tend to have positive tests, around 50% from the Middle East and Japan but fewer from western Europe and the USA. A positive test is not diagnostic for Behçet's disease.

Treatment

Unfortunately, drug treatment for NBS has a limited evidence base. Common practice at centres experienced with treating NBS is to treat acute episodes with high dose, usually intravenous, steroids for 3–7 days with many experts preferring to continue with a tapering dose of oral prednisolone over the next 3 months. Patients with relapsing or progressive NBS are usually treated with azathioprine, methotrexate or pulsed cyclophosphamide, with or without added prednisolone. Some of the newer immunomodulatory therapies such as tacrolimus, infliximab and anti-TNF-α have been tried with NBS because there is some evidence of their efficacy in controlling systemic BS symptoms. Thalidomide and colchicine are widely used for the mucocutaneous manifestations. Neurovascular disease is managed conventionally with antiplatelet agents; the role of anticoagulation remains uncertain.

Neurological aspects of pregnancy

Pregnancy is associated with a range of physiological changes including dynamic alterations in hormone levels. These changes can either change the presentation or severity of pre-existing neurological diseases, including migraine, epilepsy, multiple sclerosis and myasthenia gravis; or they may be associated with a conditions arising *de novo* during pregnancy, in particular cerebrovascular disorders. The management of epilepsy in women of childbearing age is of particular importance and is dealt with in some detail here.

Epilepsy and women of childbearing age

Fertility

Fertility rates are lower in women with treated epilepsy than in an age-matched control population. In one study of a general population of over 2 million persons in England and Wales, an overall fertility rate was found of 47.1 (95% CI 42.3–52.2) live births/1000 women with epilepsy per year compared with a national rate of 62.6. The difference in rates was found in all age categories between the ages of 25 and 39 years (Figure 25.7). There are probably several reasons for this. Women with epilepsy have low rates of marriage, marry later, suffer social isolation and stigmatization. Some avoid having children because of the risk of epilepsy in the offspring, and some because of the teratogenic potential of antiepileptic drugs. Biological factors that may be relevant include genetic influences on fecundity and adverse antiepileptic drug effects. One-third of menstrual cycles in women with temporal lobe epilepsy may be anovulatory, compared to 8% in control

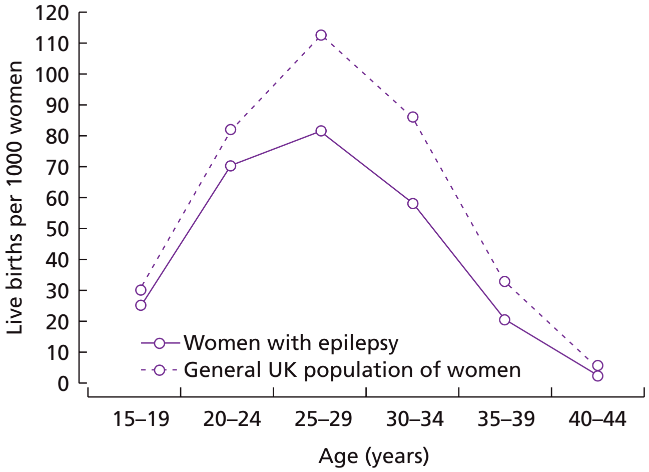

Figure 25.7 Fertility rates amongst women with epilepsy compared to that in the general population in an unselected UK population of 2,052,922 persons. From Wallace *et al.* (1998) with permission.

populations. It has been suggested that valproate results in polycystic ovarian syndrome, possibly by causing obesity, peripheral insulin resistance, hyperandrogenism and hyperinsulinaemia, although this finding has not been widely replicated.

Pregnancy

Effects of epilepsy on pregnancy and delivery

There are 3–4 live births per 1000 women of childbearing age with epilepsy in Western populations, and epilepsy is one of the most common medical conditions encountered in obstetric units. Epilepsy increases by up to threefold the risks of various common complications (Table 25.6). The perinatal mortality rate has been found to be twice that of the general population. About 1–2% of all women with epilepsy will have tonic–clonic seizures during delivery and this can clearly complicate labour. The fetal heart rate can be dramatically slowed by a seizure, and fetal monitoring is recommended during vaginal delivery. Home birth should not generally be contemplated and obstetricians are more likely to recommend caesarean section.

Effect of pregnancy on the rate of seizures

Pregnancy has a little effect on seizure frequency in most patients, although there are patients whose seizures stop only during pregnancy and others, usually with severe epilepsy, whose seizures worsen. There are a number of potential causes for changes in seizure frequency: hormonal effects, non-compliance with medication, inappropriate dose reductions, changing drug disposition and serum levels, fluid retention, vomiting, stress, anxiety and sleep deprivation.

New-onset epilepsy during pregnancy

The annual incidence of epilepsy at childbearing age is about 20–30 cases per 100,000 persons, and so the chance development of epilepsy during pregnancy is not uncommon. Occasionally, presumably because of hormonal or metabolic influences, some women experience epileptic seizures exclusively during pregnancy (gestational epilepsy) but this is a rare pattern.

Table 25.6 Complications of pregnancy reported with increased frequency in women with epilepsy.

Bleeding *in utero*
Premature separation of the placenta
Toxaemia of pregnancy and pre-eclampsia
Miscarriage and stillbirth
Intrauterine growth retardation, low birth weight
Perinatal mortality
Premature labour
Breech and other abnormal presentations
Forceps delivery, induced labour, caesarean section
Precipitant labour
Psychiatric disorders
Seizures and status epilepticus

Symptomatic epilepsy may present in pregnancy with various different underlying causes. Pregnancy can stimulate an increase in size of meningiomas because of oestrogenic stimulation, resulting in newly presenting epilepsy. Arteriovenous malformations may also present more commonly in pregnancy. The risk of ischaemic stroke increases in pregnancy. The underlying causes include arteriosclerosis, cerebral angiitis and Moyamoya disease, Takayasu's arteritis, embolic disease from a cardiac or infective source, sickle cell disease, antiphospholipid antibody syndrome, thrombotic thrombocytopenic purpura, deficiencies in antithrombin, protease C and S, and factor V Leiden. There is also a higher incidence of subarachnoid haemorrhage and of cerebral venous thrombosis. Pregnancy can also predispose to cerebral infections from bacteria (including *Listeria*), fungi (coccidioides), protozoa (*Toxoplasma*), viruses and HIV infection.

The extent of investigation of newly developing epilepsy in pregnancy will depend on the clinical setting. X-rays, and thus CT should be avoided wherever possible. There are no known risks to the developing fetus of MRI and this is the brain imaging modality of choice. In the non-urgent situation, investigation is often deferred until pregnancy is completed.

Eclampsia and pre-eclampsia

Most new-onset seizures in the late stages of pregnancy (after 20 weeks) are caused by eclampsia. Pre-eclampsia is characterized by hypertension, proteinuria, oedema, abnormalities of hepatic function, platelets and clotting parameters. About 5% of cases, if left untreated, progress to eclampsia. The eclamptic encephalopathy results in confusion, stupor, focal neurological signs and cerebral haemorrhage as well as seizures. The epilepsy can be severe and progress rapidly to status epilepticus. The incidence of eclampsia in Western Europe is about 1 in 2000 pregnancies, but it is more common in some developing countries with rates as high as 1 in 100. It carries a maternal mortality rate of 2–5% and also significant infant morbidity and mortality.

Traditionally, obstetricians have used magnesium sulphate in the treatment of seizures in eclampsia, and the superiority of magnesium over phenytoin and/or diazepam has been clearly demonstrated in recent randomized controlled studies. Not only does magnesium confer better seizure control, but there are less complications of pregnancy and infant survival is improved. Magnesium seems also to lessen the chance of cerebral palsy in low birth rate babies and has also been shown to decrease secondary neuronal damage after experimental traumatic brain injury. The mechanism by which magnesium sulphate acts in eclampsia is unclear; it may do so via its influence on NMDA receptors or on free radicals, prostacyclines, other neurochemical pathways or, more likely, by reversing the intense eclamptic cerebral vasospasm. It is possible that patients would benefit from both magnesium and a conventional antiepileptic, but this has not been investigated. Magnesium should be administered as an intravenous infusion of 4 g, followed by 10 g i.m., and then 5 g i.m. every 4 hours as required.

Management of labour

Regular antiepileptic drugs should be continued during labour. If oral therapy is not possible, intravenous replacement therapy can be given for at least some drugs. Tonic–clonic seizures occur in about 1–2% of susceptible mothers. In patients at risk, oral clobazam (10–20 mg) is useful given at the onset of labour as additional seizure prophylaxis. Fetal monitoring is advisable. Most women have a normal vaginal delivery, but sleep deprivation, over-breathing, pain and emotional stress can greatly increase the risk of seizures. Elective caesarean section should be considered in patients at particular risk. A history of status or life-threatening tonic–clonic seizures are an indication for caesarean section, and if severe seizures or status occur during delivery, an emergency section should be performed. Intravenous lorazepam or phenytoin should be given during labour if severe epilepsy develops and the patient prepared for caesarean section.

There is a maternal as well as infant mortality associated with severe seizures during delivery. The hypoxia consequent on a seizure may be more profound in gravid than in non-gravid women because of the increased oxygen requirements of the fetus, and resuscitation facilities should be immediately at hand in the delivery suite.

Vitamin K

Maternally ingested enzyme-inducing antiepileptic drugs can induce a relative deficiency of infantile vitamin-K dependent clotting factors (factors II, VII, IX and X) and protein C and S, predisposing to infantile haemorrhage, including cerebral haemorrhage. The neonate should therefore receive 1 mg vitamin K i.m. at birth and at 28 days of life. It is also sometimes recommended that the mother take oral vitamin K (20 mg/day) in the last trimester, although the evidence that this improves neonatal clotting is rather contradictory. If any two of the clotting factors fall below 50% of their normal values, vitamin K i.m. will be insufficient to protect against haemorrhage and fresh frozen plasma should be given intravenously. Similarly, if there is evidence of neonatal bleeding, or if concentrations of factors II, VII, IX or X fall below 25% of normal, an emergency infusion of fresh frozen plasma is required.

Epilepsy and the fetus

Effect of seizures on the fetus

The exact risks are not established. Clearly, in the latter stages of pregnancy, a convulsion carries the risk of trauma to the placenta and/or fetus, especially if the women falls. However, most debate has revolved around the suggestion that seizures damage the fetus through lactic acidosis or hypoxia. The hypoxia is usually very short-lived and the placenta is a well-buffered system; intuitively these risks seem likely to be small. One study has found that first trimester seizures are accompanied by a higher risk of fetal malformation than seizures at other times, although the reliability of these conclusions is in doubt. Stillbirth has been recorded after a single seizure or series of seizures, although this must be very rare. However, status epilepticus during pregnancy or delivery is extremely hazardous, and one study of status epilepticus during delivery reported a 50% infant mortality and 30% maternal mortality. Partial seizures have no known effects upon a fetus.

Teratogenicity of antiepileptic drugs

There is no doubt that some maternally ingested antiepileptic drugs carry the risk of teratogenicity. This has been shown clearly both in animals and in clinical practice. However, assessment is complicated by the fact that seizures themselves can cause malformations, although this effect is probably small. Also social, dietary and socio-economic factors all increase the risk both of epilepsy and of malformations. Evidence is therefore difficult to assess, and accurate clinical advice difficult to give.

Major malformations associated with antiepileptic drugs

The most common major malformations associated with traditional antiepileptic drug therapy (phenytoin, phenobarbital, primidone, benzodiazepines, valproate, carbamazepine) are cleft palate and cleft lip, cardiac malformations, neural tube defects, hypospadias and skeletal abnormalities. Polytherapy carries higher risks than monotherapy, and the individual risks of some drugs has not been fully established. Phenytoin as monotherapy has a relatively low incidence of major defects although earlier studies with the drug in polytherapy showed much higher levels. One particular association is the increased risk of neuroblastoma although the absolute risk is very small. One study purported to demonstrate smaller head circumference in babies of mothers on carbamazepine, but the statistical basis of this observation was not well founded. It is unclear whether or not the benzodiazepines carry any teratogenic potential, although there are case reports of facial clefts, cardiac and skeletal abnormalities. The risk of spina bifida has been particularly well studied. The background population risk of spina bifida is approximately 0.2–0.5% with geographic variation. Valproate is associated with a 1–2% risk of spina bifida aperta, a risk that is strongly dose-related. Carbamazepine carries a risk of spina bifida aperta of about 0.5–1%. It is instructive to note that the induction of neural tube defects by valproate, and to a lesser extent carbamazepine, were not noticed initially during animal toxicology testing.

Other developmental abnormalities

In addition to the major malformations, less severe dysmorphic changes occur ('fetal syndromes'), although there is little agreement about their frequency or indeed in some cases their existence. The fetal phenytoin syndrome was the first to be described, and is said to consist of a characteristic pattern of facial and limb disturbances (Table 25.7). However, most of these features are minor and overlap with the normal variation seen in children born to healthy mothers. Recent prospective and blinded studies have shown that only hypertelorism and distal digital hypoplasia occurred at any greater frequency, and even these associations are weak. Furthermore, the nail hypoplasia tends to disappear during childhood. Cases of a 'carbamazepine syndrome' are reported with cranio-facial abnormalities, growth retardation, neural tube defects and fingernail hypoplasia. Reports of primidone and phenobarbital 'syndromes' have been published, consisting of facial changes and developmental delay. The problem is further complicated by the confounding influences of socio-economic and genetic factors. Recent interest has focused on a 'valproate syndrome' said to occur in up to 50% of infants born to mothers on valproate; again no blinded studies have been carried out and the true status of this syndrome is quite unclear.

One report has suggested that children exposed to valproate monotherapy have significantly lower verbal IQ scores when compared with children exposed to carbamazepine or phenytoin monotherapy. However, this finding has not been replicated consistently and the current status in this regard of valproate remains uncertain.

The teratogenic effects of most of the newer antiepileptic drugs have not been established. This does not imply safety, however, and three points from experience with traditional therapies are worth making. First, even today, the full range of the teratogenicity has not been not established. Second, the risk of even major malformations were not noticed until the drugs had been in extensive use for decades. Third, negative animal results are not a reliable indicator of safety.

Table 25.7 Fetal anticonvulsant syndromes. This is a list of reported abnormalities, although many are uncontrolled observations and the frequency of the anomalies is unclear. Genetic, environmental and socio-economic factors may also have a role in their development.

The following features are recorded in 'fetal anticonvulsant syndromes'

Growth
Prenatal and postnatal growth deficiencies
Microcephaly

Cranio-facial
Short nose, low cranial bridge
Hypertelorism
Epicanthic fold
Strabismus and other ocular abnormalities
Low-set ears and other aural abnormalities
Wide mouth, and prominent lips
Wide fontenelles
Cleft palate and cleft lip

Limbs
Hypoplasia of nails
Transverse palmar crease
Short fingers
Extra digits

Cerebral
Learning disability
Developmental delay

General
Short neck, low hairline
Rib, sternal and spinal anomalies
Widely spaced hypoplastic nipples
Hernias
Undescended testes
Neuroblastoma and neural ridge tumours
Cardiac and renal abnormalities
Hypospadias
Neural tube defects

Puerperium

Maternal seizures and antiepileptic drug doses

There is an increased risk of seizures in the puerperium. Clobazam 10 mg taken during delivery and for a few days after delivery can be useful to prevent seizures in this vulnerable period. If antiepileptic drug dosage has been increased because of falling levels during pregnancy, the dose should be reduced in the first week after delivery to its previous levels. Drugs circulating in the mother's serum cross the placenta. If maternal antiepileptic drug levels are high, the infant may experience drowsiness or withdrawal symptoms and neonatal serum levels should be measured in cases at risk.

Breastfeeding

The concentration of most antiepileptic drugs in breast milk is less than 30% that of plasma; although exceptions are lamotrigine, levetiracetam and phenobarbital. Furthermore, even if a drug is present in significant concentrations in breast milk, the amount ingested by the infant is usually much less than would normally be considered needed for clinical effects. Only lamotrigine, levetiracetam and phenobarbital require special precautions.

Maternal phenobarbital ingestion is a particular problem, as in neonates the half-life of phenobarbital is long (up to 300 hours) and the free fraction is higher than in adults; neonatal levels can therefore sometimes exceed maternal levels.

Maternal epilepsy

A mother at risk from seizures with altered consciousness should not be left alone with a small child. There is a danger of dropping the child or leaving the child unattended, and maternal epilepsy probably poses a greater risk to infants and toddlers than to the fetus. Sensible precautions should be taken. These might include avoiding carrying the child unaccompanied, changing and feeding the infant at ground level, and bathing the infant only when someone else is present.

Reducing risks of pregnancy to mother and child

Preconception review of drug therapy

The patient's antiepileptic drug regimen should be reviewed if possible before conception is contemplated, as many major malformations are established within the first 8 weeks of pregnancy.

It is important to establish whether antiepileptic therapy is needed at all. This will be an individual decision, based on the risks of teratogenicity against the risks of worsening epilepsy. If tonic–clonic seizures are occurring, it is usual to continue drug therapy, as such seizures carry significant risk to mother and child. However, some women with partial or non-convulsive seizures will elect to withdraw therapy even if seizures are active or likely to become more frequent. Conversely, other women who are seizure-free will wish to continue therapy because of the social and physical risks of seizure recurrence.

Drug therapy during pregnancy

In some patients, it is reasonable to withdraw therapy for the first half of pregnancy and then to reinstate the drugs; this approach is based upon the fact that the teratogenic risk is greatest in the first trimester and the physical risk of seizures greatest in the later stages of pregnancy. The relative risks need to carefully assessed, however, and a specialist review is needed before embarking upon this unusual course.

If the woman elects to continue therapy, it is best to strive for monotherapy and to aim for the minimum effective dose. A few women with severe epilepsy will need combination therapy, but this should be avoided wherever possible. It is useful to measure the serum drug concentrations that give optimal control of the epilepsy before conception. These values form a useful starting point on which to base subsequent drug dosage adjustments. Valproate should be given in the slow-release form and dosage regimens of all drugs can be changed to two or three times daily regimens to minimize blood level peaks.

Dose increases of lamotrigine (and to a lesser extent carbamazepine and phenytoin and phenobarbital) may be necessary as serum antiepileptic drug levels can fall in the second half of pregnancy. The mechanisms of the changing dose reqirement include reduced drug absorption, reduced serum albumin, protein binding changes, increased clearance and fluid retention. Levels of lamotrigine can be halved and monthly blood level estimations are recommended.

Screening for fetal malformations

Some malformations can be detected by prenatal ultrasound screening. If therapeutic termination of pregnancy is acceptable, screening procedures should include, where appropriate, a high quality ultrasound scan at 10, 18–20 and 24 weeks, measurement of α-fetoprotein levels and amniocentesis. About 95% of significant neural tube defects can be detected prenatally, as well as cleft palate and other midline defects, and major cardiac and renal defects. However, the mother should be informed that not all malformations are detectable even with the most sophisticated screening methods.

Folic acid supplementation

The fetus of an epileptic women is at a greater than expected risk of a neural tube defect, particularly if the mother is taking valproate. A recent Medical Research Council trial of folic acid supplementation during pregnancy showed a 72% protective effect against neural tube defects in women who had conceived a fetus previously with neural tube defects. Although there has been no specific study in epilepsy, it would seem reasonable for all epileptic women to be given folic acid supplementation during pregnancy. A dose of at least 4 mg/day is recommended on an empirical basis, as lower doses may not fully restore folate levels. Folic acid supplementation is generally recommended, in any event in all women who may become pregnant.

Cerebrovascular disorders in pregnancy

Pregnancy is associated with an increased risk of ischaemic and haemorrhagic stroke. Ischaemic stroke in pregnancy is caused by arterial occlusion in about two-thirds of cases (most often in the middle cerebral artery territory), and venous occlusion of cortical veins or venous sinuses in the remaining third. Thus, venous events are over-represented in pregnancy and a high index of suspicion is required. Arterial stroke is most often in the third trimester or in the first week postpartum. Venous sinus thrombosis is most common in the first 2 weeks postpartum but can occur in the third trimester; presentation differs from arterial stroke in that headache, seizures and behavioural changes may be prominent, in addition to focal neurological symptoms.

Cerebral haemorrhage in pregnancy may be caused by pre-existing aneurysm or arteriovenous malformation, or in association with venous infarction or uncontrolled hypertension (e.g. in the context of eclampsia). Rupture of arteriovenous malformations is most common in the second trimester, while there is no particular peak timing for aneurysmal haemorrhage. There is no evidence that vaginal delivery increases the risk of rupture from arteriovenous malformation or aneurysm; decisions on the method of delivery should be based on obstetric factors.

Pre-eclampsia is a disorder defined by pregnancy-associated proteinuria and hypertension with multisystem involvement (renal, hepatic, neurological). The neurological manifestations include seizures (usually generalized without focal features), visual disturbance and reduced conscious level. These symptoms require urgent investigation to exclude intracranial haemorrhage or other vascular causes. Treatment of hypertension and of seizures with intravenous magnesium is appropriate, sometimes with conventional anticonvulsant drugs.

Specific neurovascular syndromes associated with pregnancy include posterior reversible leucoencephalopathy syndrome (PRES) and cerebral vasoconstriction syndrome (Call–Fleming syndrome). PRES characteristically occurs in the first postpartum week, and is characterized by seizures, uncontrolled hypertension and visual symptoms. The pathophysiology is thought to be disruption of the blood–brain barrier, perhaps because perfusion exceeds the autoregulation threshold. The predilection for the posterior circulation is suggested to result from a reduced sympathetic innervation compared to the anterior circulation. The symptoms of PRES mimic those of cerebral venous sinus thrombosis and eclampsia; neuro-imaging is essential to make an accurate diagnosis. In PRES the findings on MRI are characteristic, showing altered signal in the occipito-parietal regions, usually without a major component of restricted diffusion on diffusion-weighted MRI in contrast to acute ischaemia (Figure 25.8). Urgent treatment is required for the hypertension and seizures; good recovery is the rule if treatment is started promptly. The imaging abnormalities usually resolve, and if this is the case and ongoing seizures have not occurred then anticonvulsants can be stopped. It has been suggested that the term PRES be abandoned because the condition is not only posterior in location, not always reversible and not always associated with encephalopathy.

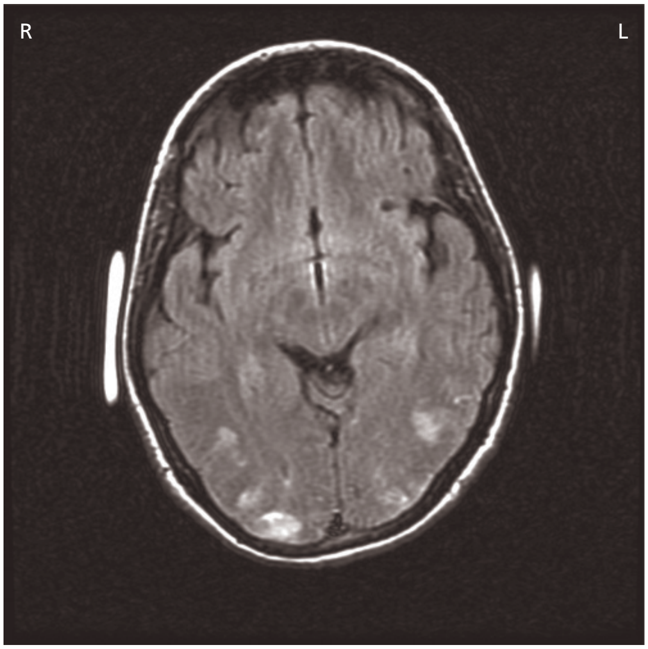

Figure 25.8 Case of PRES: axial FLAIR MRI of a 17-year-old woman who presented with seizures and complete visual loss in the context of uncontrolled hypertension 1 week after delivery. Note patchy high signal abnormalities bilaterally in the parieto-occipital regions. One month later these imaging abnormalities had fully resolved.

Call–Fleming syndrome (cerebral vasoconstriction syndrome) is commonly observed in the postpartum period and clinically causes a thunderclap headache followed by focal neurological deficit. Definitive diagnosis requires the demonstration of vasospasm on angiographic imaging. Areas of ischaemic change may be seen on MRI as infarction may result from vasospasm. There is clearly potential overlap and lack of firm diagnostic criteria for both PRES and Call–Fleming syndrome, and there is a need for further clarification of these diagnostic terms.

Pregnancy and other neurological diseases

Pituitary disorders

Pregnancy causes the pituitary gland to enlarge. Sheehan's syndrome is a rare condition of pituitary infarction, usually caused by postpartum haemorrhage and systemic hypotension, or by the vascular demands of an enlarging pituitary gland exceeding the available vascular supply. Infarction may transform into haemorrhage. In some cases, primary haemorrhage arises in an enlarged pituitary for reasons that are unclear. Infarction or haemorrhage can result in acute pituitary insufficiency and shock, hence the term pituitary apoplexy.

Lymphocytic hypophysitis is thought to be of autoimmune origin and usually self-limited. If the pituitary enlargement is causing symptoms, e.g. visual loss, then corticosteroids may be indicated.

Headache

Migraine is reported to improve in up to 80% of cases during pregnancy, presumably because of altered oestrogen levels. However, because migraine is so common, there are large numbers of women with significant migraine requiring treatment during pregnancy. Headache arising for the first time in pregnancy is of greater concern and may require further investigation. If migraines are frequent and disabling then propranolol can be used in pregnancy. Paracetamol is the safest acute treatment. Ergotamine is contraindicated and there is insufficient information on the safety of triptans to recommend them in pregnancy. The most common type of headache in pregnancy is tension-type headache.

Neuromuscular disorders

Restless leg syndrome affects up to 30% of women during the third trimester. Oral folate reduces the frequency of symptoms. Pregnancy has an unpredictable effect on myasthenia gravis, with no particular trend for worsening or improvement in symptoms. Bell's palsy is several times more common in pregnancy and the puerperium than at other times. Carpal tunnel syndrome affects about one-fifth of patients in the third trimester and is likely to resolve after delivery. Meralgia paraesthetica can occur late in pregnancy because of stretching or compression of the lateral cutaneous nerve of the thigh and can be expected to improve following delivery. Gestational polyneuropathy may be related to nutritional deficiency because of general malnourishment or hyperemesis gravidarum. The latter can also cause Wernicke's encephalopathy. Damage to the nerves of the lumbosacral plexus is a rare complication of delivery, particularly if there are complicating factors including cephalopelvic disproportion, shoulder dystocia or instrumentation with forceps. Neurological complications of epidural anaesthesia are rare.

Multiple sclerosis

Unless there are complicating factors (e.g. severe motor disability and contractures) multiple sclerosis has no known effects on fertility, pregnancy, recommended mode of delivery, congenital malformations or perinatal death rates. Overall, pregnancy does not affect the frequency of MS relapses or rate of disease progression. There are no studies of the efficacy or safety of disease-modifying agents including the interferons and glatiramer acetate in pregnancy. Corticosteroids may be safely used to treat relapses of multiple sclerosis in pregnancy.

Chorea gravidarum

Chorea gravidarum (CG) simply refers to any type of chorea occurring in pregnancy. The term does not imply a specific cause; this condition is a clinical syndrome not a distinct disease. About one-third of patients have a history of rheumatic fever or Syndenham's chorea. It is therefore speculated that CG results from the reactivation of previous subclinical basal ganglia damage; the mechanism may involve ischaemia or increased dopamine sensitivity mediated by elevated hormone levels during pregnancy. CG may be secondary to other known causes of chorea including Syndenham's chorea, lupus or Huntington's disease. CG seldom requires drug treatment. If CG is mild the patient may even be unaware of the involuntary movements. Drug treatment is only used if its severity puts the mother or fetus in danger, e.g. because of poor nutrition, disturbed sleep or injury. If treatment is necessary dopamine blockers including haloperidol may be used.

Tumours

Overall, brain and spine tumours are no more common in pregnant than non-pregnant women of similar age. Meningiomas present more often than expected by chance during the second half of pregnancy as they may enlarge because of the effects of changes in circulating oestrogen levels on tumour oestrogen receptors. The symptoms of meningiomas may improve spontaneously postpartum, so that treatment can often be delayed until after delivery. However, surgery for large or aggressive brain tumours during pregnancy may be needed urgently if there are signs of raised intracranial pressure or papilloedema. Most women with brain tumours presenting in pregnancy are managed by caesarean section to avoid possible cerebral herniation during labour. Choriocarcinoma is a malignancy seen in pregnancy and often metastasizes to the brain. Pituitary adenomas are slightly more common in pregnancy and large tumours may be associated with the onset of visual failure; careful visual field assessment is therefore mandatory in every pregnant woman presenting with new headache symptoms.

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension is more common during pregnancy than at other times, and often presents in the second trimester. If already present it usually deteriorates in pregnancy. Treatment is guided by close monitoring of visual function including visual fields. Weight control is recommended. A short course of corticosteroids may be considered, along with serial lumbar puncture or more invasive procedures including lumboperitoneal shunting or optic nerve fenestration if vision is threatened. The teratogenic potential of acetazomlamide is unknown, but it is usually avoided in the first trimester.

Acknowledgement

Dr Jeremy Levy, consultant nephrologist, Hammersmith Hospitals, London gave most helpful guidance on the section on vasculitides.

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Neurology: A Queen Square Textbook Edited by Charles Clarke, Robin Howard, Martin Rossor and Simon Shorvon © 2009 Blackwell Publishing Ltd.
ISBN: 978-1-405-13443-9

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